The Milbank Memorial Fund

QUARTERLY

CONTENTS

Vol. XXIV APRIL 1946 No. 2

Edited by the Technical Staff

Published quarterly by the MILBANK MEMORIAL FUND, 40 Wall Street, New York 5, New York. Printed in the U.S.A. Subscription $1.00 a year.

IN THIS ISSUE

THE fourth paper in the series of reports on an investigation of "Nutritional Status of Aircraft Workers in Southern California" discusses "Effects of Vitamin Supplementation on Clinical, Instrumental, and Laboratory Findings, and Symptoms." This report by Dr. Henry Borsook, Jacob Dubnoff, Geoffrey Keighley, and Dorothy G. Wiehl describes the diagnostic procedures used in an examination to detect nutritional deficiencies in over five hundred persons, half of whom were given a six-vitamin and calcium supplement and the other half a placebo for nine to twelve months, and compares these two groups with respect to their nutritional status before and after the administration of supplements.

Evidence of the effect of therapy on modification of physical or anatomical signs noted before therapy was begun or on differences between therapy and placebo subjects at the end of the therapy period with respect to prevalence of various signs is evaluated for the following: vitamin A deficiency—follicular hyperkeratosis and loss of conjunctival transparency; thiamin deficiency—abnormalities in reflexes, calf muscle tenderness, plantar dysesthesia, and loss of vibratory sensibility; riboflavin (or vitamin B complex) deficiency—cheilosis and other skin manifestations, and corneal vascularization; niacin (or vitamin B complex) deficiency—tongue abnormalities. At the end of the therapy period, persons who had received vitamins had a lower prevalence of follicular hyperkeratosis and of tongue abnormalities and had a greater improvement in conjunctival transparency than those who received placebos. For these signs, the data are suggestive of a positive therapeutic effect, but for all others there was no evidence of any response to therapy. Medical histories obtained at the end of the Study also showed no symptomatic superiority for persons who received the vitamin supplement.

• • •

Numerous writers have noticed that Latin America is more disposed to urban living than other regions with a similar paucity of industry. But no comprehensive study has been made of this tendency. An effort in this direction has been made by Dr. Kingsley Davis and Miss Ana Casis in their study "Urbanization in Latin America," the first part of which appears in this issue. In this first article the authors relate the growth of cities to regional differences and problems in Latin America. They consider the causes and consequences of urban expansion and give some special attention to the situation in Argentina. The second part, scheduled for a later issue, considers certain basic characteristics of city, as contrasted with rural, populations in Latin America. The study affords a contribution to Latin American demography and sociology.

NUTRITIONAL STATUS OF AIRCRAFT WORKERS IN SOUTHERN CALIFORNIA

IV. EFFECTS OF VITAMIN SUPPLEMENTATION ON CLINICAL, INSTRUMENTAL, AND LABORATORY FINDINGS, AND SYMPTOMS[1]

HENRY BORSOOK[2], JACOB W. DUBNOFF[2], GEOFFREY KEIGHLEY[2], DOROTHY G. WIEHL[2], WITH THE ASSISTANCE OF ELIZABETH B. GOOLDEN[3] AND JOSEPHINE G. WILLIAMS[3]

THIS is the fourth report on a Study of the nutrition of aircraft workers in Southern California. The first report (1) described and analyzed the diets of the subjects at the beginning of the Study (November 1941 - February 1942). The second (2) presented data on initial nutritional status as determined by clinical, instrumental, and laboratory examinations. The third (3) compared the workers in this Study with the general industrial population at the time, and described the effects of vitamin supplementation for one year on absenteeism, termination rates, and work performance as determined by Merit Review Scores. The third report also described the following

[1]This Study of the nutrition of aircraft workers in California was sponsored by the Nutrition Committee (R. A. Millikan, Chairman), appointed by the Board of of Supervisors of the County of Los Angeles, California, and the Committee on the Nutrition of Industrial Workers of the National Research Council. The Study was supported in part by the sponsors and by the following: the California Institute of Technology, The Lockheed Aircraft Corporation, the Milbank Memorial Fund, the War Production Board, and the Work Projects Administration (Project No. 12372). Support was also received from the California Fruit Growers Exchange, the Gelatin Products Corporation, Hoffman-La Roche, Inc., Merck and Company, the National Oil Products Company, the Research Corporation, E. R. Squibb and Sons, and the Vita-Food Corporation.

Dr. L. de Merre participated in this work; we take this occasion to thank him.

[2]California Institute of Technology, Pasadena.

[3]Milbank Memorial Fund, New York.

At the second examination H. Borsook made the physical examinations, biomicroscopic examinations of the tongue and conjunctivae; J. W. Dubnoff made the biomicroscopic examinations for corneal vascularization; and G. W. Keighley conducted the tests for vibratory sensibility. At the first examination the physical examinations were made by Elmer Alpert and E. D. Kremers; biomicroscopic examinations on the eyes by Elmer Alpert, H. Borsook and J. W. Dubnoff. Miss B. T. Woodberry performed the hematological work at the first examination and Elizabeth B. Goolden at the second. The ascorbic acid measurements were made by G. H. Palmer at the first examination and by Josephine G. Williams at the second. Dorothy G. Wiehl supervised and participated in the analysis of all the data, as well as in planning the Study.

features of the Study: the nature of the vitamin supplement and of the placebo given the Vitamin and Placebo groups, respectively, the selection and composition of the Vitamin and Placebo groups, and of a second control group selected to appraise the psychotherapeutic, as distinguished from the therapeutic, effect of the vitamin supplement; and it compared the diet histories at the beginning and at the end of the Study.

This fourth report presents the clinical, instrumental, and laboratory findings at the end of a year's vitamin or placebo supplementation. It compares the findings in the two groups at the end of the Study, and also compares the findings for each group with those immediately before the supplementation was begun. It appraises, on the basis of these data, the effects of the vitamin supplement on physiological and anatomical conditions used for the appraisal of nutritional status, and the psychological effects of the vitamin supplement and of the placebo.

The Nature of Vitamin Supplement and Placebo

The formula for the nutritional supplement, consisting of vitamins and calcium in tablets and capsules, was prescribed by the Committee on the Nutrition of Industrial Workers of the National Research Council. Its composition was as follows:

Vitamin A (from fish liver oil)	50,000 I.U.
Vitamin D (from fish liver oil)	800 I.U.
Vitamin B_1 (synthetic)	10 mg.
Vitamin B_2 (synthetic)	10 mg.
Niacinamide (synthetic)	100 mg.
Ascorbic Acid (synthetic)	250 mg.
Calcium ($Ca\ CO_3$)	500 mg.

These amounts of vitamins and calcium, divided into two equal doses, were given five days a week for a year. The recipients of the vitamin-mineral supplement are designated the Vitamin group.

A Placebo group was given tablets containing sodium bicarbonate, some colored to resemble riboflavin, and corn oil capsules to simulate those containing vitamins A and D.[4]

Composition of the Vitamin and Placebo Groups

All the subjects of the Study were volunteers, and all were white males working on the swing shift in all major departments of the plant. As they reported for their first physical examination they were assigned alternately either to the Vitamin or to the Placebo group. Feeding of the full vitamin supplement, as described above, began March 1, 1942, and continued throughout the Study year. During the year some of the men were transferred to the day shift. These are included without segregation in the tabulation of results.

The second examination began in the ninth month of the Study. Consequently, some of the subjects had been receiving the supplement for only this period at the time of their second examination. The minimum number of the days on which the vitamin supplement was received by a subject included in the following analysis was 180, and 14.9 per cent of the Vitamin group received therapy for 180 to 215 days[5] before the second examination. It is felt that therapeutic effects would have manifested themselves in some degree by this time; and that the difference, in these respects, between nine and twelve months of supplementation would not be large. Fifty-three per cent of the group received therapy for 237 to 270 days, the latter being the maximum for any subject. Hence all subjects who had been examined at the beginning and end of the Study, and who had been receiving the vitamin supplement or placebo for nine

[4]The preceding report (3) describes the method of distribution and the measures taken to insure that the tablets and capsules were taken.

[5]These are the numbers of days on which therapy was given, that is, the two days a week on which therapy was not distributed and the days absent for any reason are deducted from the elapsed number of days between March 1, 1942 and the date of the second examination.

months or more are included in the tabulation of results. The number of subjects was about half those who began the Study. The losses were the result mainly of terminations and transfers. These are explained in detail in the preceding report (3).

In this report, which is concerned chiefly with the therapeutic effects of the vitamin supplement, no distinction is made between direct production workers and clerical or supervisorial staff. In other words, all the subjects in the Vitamin and Placebo groups, respectively, are considered together. It seems improbable that the type of occupation could have been a significant factor in determining whether or not a positive therapeutic effect appeared, because, for the great majority, the work was not heavy and there were no occupational hazards such as high temperature, very high or very low humidity, or exposure to toxic chemicals.

Table 1. Age distribution of aircraft employes in the Vitamin and Placebo groups with first and second examinations.

Age Group	Per Cent of Total	
	Placebo Group	Vitamin Group
TOTAL	100.0	100.0
19–24 Years	37.5	37.8
25–29	32.1	29.0
30–34	18.9	17.6
35–39	5.4	8.8
40–49	6.1	6.8
Number of Men	259	262

The Vitamin and Placebo groups are very similar in age composition as is shown in Table 1.* About 70 per cent of the men in each group was under 30 years of age and only 6 to 7 per cent was 40 to 50 years of age at the beginning of the Study. Thus, the population in the Study was largely of young men.

The quality of the diets at the end of the Study year was practically the same as at the beginning and there was no marked difference in the diets of the two groups (3).

*The numbers of subjects vary slightly for different procedures in the examination because a few persons did not receive a complete examination at the first or second examination.

Diagnostic Procedures

Before the Study was begun, it was expected that no cases of severe or acute severe nutritional deficiency would be found. Accordingly, diagnostic procedures were chosen which held out some promise of detecting mild as well as severe nutritional deficiency. The procedures used on the first examination were: medical and diet histories, physical examination with special reference to evidence of nutritional status, biomicroscopic examination of the conjunctiva and cornea, examination of the blood for syphilis, hemoglobin, cell volume, red cell count, serum albumin, and plasma ascorbic acid.

As expected, no cases of severe or acute nutritional deficiency were found. Also, as expected, our experience in the first examination suggested some additions to or refinements of the examination procedures for the purpose of better detection of mild deficiency states or of making some of the procedures more quantitative. It seemed also that we might safely omit determination of serum albumin on the second examination since all the values on the first examination were within the normal range. The protein intake was adequate, and there was no reason to believe it was likely to become worse.

Accordingly, the second examination consisted of all the procedures used in the first examination except the determination of serum albumin, and the following additions: more detailed examination of the skin, quantitative measurement of vibratory sensibility in the toes, more quantitative record of corneal vascularity, biomicroscopic examination of the tongue, and routine urinalysis.[1]

We recognized that the employment of additional or more

[1]On the first examination of 1,205 men examined for syphilis, there were two positives and two questionably positive. On the second examination the two positive cases were again positive, the two questionably positive were lost to the survey; there were no others either positive or questionably positive.

There were no notable findings in the urinalyses of either the Placebo or Vitamin groups.

elaborate procedures in the second examination would be of only limited value to our main purpose. Firm conclusions regarding the therapeutic effect of the vitamin supplement could be drawn only from rigorously comparable data obtained from examinations made at the beginning and again at the end of the Study period. Nevertheless, we felt that some appraisal of the effect of the vitamin supplement might be made from the data obtained by the procedures used only at the second examination. The Vitamin and Placebo groups were initially closely similar (*see* (3) and the tables below). Therefore, no difference between the Vitamin and Placebo groups at the end of the Study would indicate that the vitamin supplement had been ineffective and a statistically significant difference would suggest (it would not prove) that it had had some effect. The nature of the effect would be defined fairly precisely and would provide a basis for adequately controlled experimental tests.

One other unavoidable circumstance limited the number of instances in which strict comparisons could be made between the first and second examinations; except for the biomicroscopic examinations, the observers were different on the two examinations. Where the procedures were not measurements but nonquantitative appraisals, the criteria used by the different examiners on the two examinations were so different in some instances as to invalidate comparisons between the first and second examinations. The data thus obtained fall into the same class, as far as appraising the effect of the vitamin supplement is concerned, as those from procedures used only on the second examination.

Vitamin A Deficiency: Skin Conditions

Follicular hyperkeratosis of the skin was proved to be a sign of vitamin A deficiency by Frazier and Hu (4) and by Loewenthal (5) independently, by the effectiveness of cod liver oil ther-

apy (4), of an oil rich in vitamin A and free of vitamin D (5), and of carotene (6).

Many of our subjects had a skin condition which resembled in milder degree the follicular hyperkeratosis described by Frazier and Hu and by Loewenthal.

The gross and histopathology of the latter condition, its characteristic distribution on the skin, the variation in incidence at different ages, and the course of response to therapy were described by Frazier and Hu and their collaborators (6, 7, 8). A summary of their findings is presented here because of their bearing on the question whether the condition seen in our subjects was related to that which they described and whose relation to vitamin A deficiency is proved.

At first, the skin becomes dry and slightly rough. Spinous papules then appear at the sites of the hair follicles. These are keratotic plugs of the hair follicles; they can be expressed, leaving a small hole, which gradually refills. The papules vary in size, the largest 5 mm. in diameter, hemispherical, rather firm, and usually deeply pigmented, with a hyperpigmentation extending beyond the base of the papule. On histological examination there is seen a hyperplasia and hyperkeratinization of the epithelium of the epidermis and of the hair follicles, and keratinization of the epithelium of many sweat gland ducts. The mouth of the affected hair follicle is greatly dilated and occluded by dense masses of horny substance arranged in approximately concentric lamellae. Coiled atrophic hairs are sometimes found below the follicular plugs. The mouths of many sweat gland ducts are similarly dilated and occluded by conical masses of keratinous material.

The antero-lateral aspects of the thighs and the postero-lateral aspects of the upper part of the forearms commonly are affected first. The eruption gradually spreads to the extensor surfaces of both upper and lower extremities, the shoulders, lower part of

the abdomen, and to a lesser extent to the chest and buttocks. The eruption is usually abundant and symmetrical; occasionally the lesions are few and widely scattered, or more rarely restricted to a single area.

In some, but not all, cases the follicles may be indurated, and still less frequently pustulated. In some cases there may be many comedones on the face at the sites commonly involved in acne; but unlike acne, the skin of the face may be dry and without the excessive sebaceous secretion of acne.

On a good diet supplemented by 30 cc. of cod liver oil daily, the ocular keratomalacia improved first and was considered cured in a few weeks; but treatment for several months was required for the skin to regain its normal appearance. Even then a few spinous papules and some hyperpigmentation remained.

The age distribution of follicular hyperkeratosis reported has varied. Frazier, *et al.* have reported that follicular hyperkeratosis was very frequently a concomitant of xerophthalmia and keratomalacia in hospitalized patients aged 15 to 30 years and seldom present in younger or older patients (7) and that most of their hyperkeratosis cases without these ocular lesions were young adults. Among children with these ocular lesions, a general xerosis of the skin which improved on administration of vitamin A was noted frequently. From these and later observations (8), these authors have suggested that the skin lesion progresses with increasing age and that during adolescence the follicular lesions attain their greatest magnitude. This age variation in the severity of the cutaneous lesion is mentioned also by Loewenthal (9) who surveyed children and young adults in native schools in Uganda, Africa. However, Loewental found a greater prevalence of "follicular eruption" among children than among adults and a greater prevalence in children before puberty than after puberty. In this population, the prevalence of xerophthalmia was less than 5 per cent.

Loewenthal (5) was unable to distinguish the acneform condition of the face from that in acne vulgaris. He described induration of the papules, but no cases of pustulation.

In their latest publication (8), Frazier, *et al.* caution against the conclusion that all cases of follicular hyperkeratosis are the result of vitamin A deficiency.

Steffens, Blair, and Sheard (10) produced follicular hyperkeratosis in a human subject maintained for 190 days on a diet extremely deficient in vitamin A (100 to 300 I.U. daily). After seventeen days' administration of 80,000 units of vitamin A daily, the skin was normal except for keratotic plugs in the hair follicles. The follicular hyperkeratosis appeared before impairment of dark adaptation could be detected instrumentally.

Moult (11) and Sullivan and Evans (12) produced the same histological picture as that described by Frazier and Hu in the skin of rats by diets restricted in, but not devoid of, vitamin A.

The clinical findings, including the response to vitamin A therapy, of Frazier, *et al.* and of Loewenthal have been confirmed by Sweet and K'Ang (13), Youmans (14, 15), Lehman and Rapaport (16), Straumfjord (17, 18) and Saunders (19).

Vitamin A has been reported to be specific, or a useful adjuvant to therapy in several other disturbances of the eye or skin; in follicular conjunctivitis (20); in keratosis follicularis (Darier's Disease), where the dark adaptation may be normal, though it is often subnormal (21, 22, 23, 24); in an abnormal perifollicular brown pigmentation of the limbs (25); in nummular eczema (26); and in infective lesions of the skin in infants (27). Mashkilleison, *et al.* (28) reported beneficial results from vitamin A therapy in Devergie's Disease, keratosis follicularis, and seborrheic eczema. Kohn, *et al.* (29) reported a placebo-controlled experiment on the effect of a poly-vitamin supplement containing 5,000 I.U. vitamin A given British school children for thirty-seven weeks. They gained the impression

that the skins of the vitamin group were "clearer, smoother, and sleeker" but they could not define the difference more definitely.

Follicular hyperkeratosis also occurs in scurvy (30); and the lesions are indistinguishable from those in vitamin A deficiency (31). But scurvy was certainly absent in the cases dealt with in the reports cited above and in our subjects.

The foregoing review of the literature (it is by no means complete) shows that the skin is the site of a number of lesions benefited by vitamin A therapy; and that these lesions may occur in

Table 2. Prevalence of conditions or signs attributed to vitamin A deficiency noted by examiners for persons in Placebo and Vitamin groups [1] at first and second examinations.

Condition	Number of Cases				Per Cent of Total Examined			
	First Examination		Second Examination		First Examination		Second Examination	
	Placebo	Vitamin	Placebo	Vitamin	Placebo	Vitamin	Placebo	Vitamin
Hair: Number of Persons Examined			260	257			100.0	100.0
Dryness	*	*	95	70			36.5*	27.2
Skin: Number of Persons Examined	255	258	259	262	100.0	100.0	100.0	100.0
Face:								
Follicular Hyperkeratosis	0	0	55	37	0	0	21.2*	14.1
Acne	12	5	7	4	4.7	1.9	2.7	1.5
Comedones	*	*	16	11			6.2	4.2
Roughness, Dryness	1	1	3	1	0.4	0.4	1.2	0.4
Body:								
Follicular Hyperkeratosis	1	7	211	173	0.4	2.7*	81.5**	66.0
Acne	4	3	5	2	1.6	1.2	1.9	0.8
Seborrhea, Sebaceous Plugs	2	0	9	4	0.8	0	3.5	1.5
Comedones	*	*	31	20			12.0	7.6
Roughness, Dryness	2	3	79	53	0.8	1.2	30.5**	20.2
Total Persons With One or More Skin Signs	16	16	228	193	6.3	6.2	88.0**	73.7

* Hair dryness and comedones were not recorded on first examination.

[1] A prevalence rate for one group which is higher than that for the other group by a statistically significant amount is designated as follows: * after rate indicates that the probability of the observed difference occurring from chance is less than five and more than one in a hundred, and ** indicates the probability is less than one in a hundred.

the absence of xerophthalmia or keratomalacia, of night blindness, or of impaired dark adaptation when measured instrumentally.

In the second examination of subjects in this Study, the examination of the hair and skin was greatly refined for the purpose of detecting milder deficiency states than were noted in the first examination. In the second examination we recorded whether or not the hair seemed abnormally dry, and any degree, no matter how slight, of follicular hyperkeratosis. For the latter condition, the examiner noted the location and extent of skin area involved, and whether or not the hyperkeratotic follicles were pigmented, had protruding plugs, were indurated, or infected. In the first examination, only severe follicular hyperkeratosis was recorded and the hair was not examined.

The prevalence of dryness of hair and of follicular hyperkeratosis in the Vitamin and Placebo groups is shown in Table 2. Dry hair was significantly more frequent in the Placebo than in the Vitamin group, 37 as against 27 per cent. The criterion used for dryness was not well defined, and this difference between

Table 3. Prevalence of follicular hyperkeratosis noted on different areas of the body at second examination.

Follicular Hyperkeratosis and Area in Which it Was Observed	Number		Per Cent		P[1]
	Placebo	Vitamin	Placebo	Vitamin	
Total Persons Examined	259	262	100.0	100.0	
No Follicular Hyperkeratosis	44	84	17.0	32.1	<.001
Any Follicular Hyperkeratosis	215	178	83.0	67.9	<.001
Face	55	37	21.2	14.1	.02–.05
Trunk	187	151	72.2	57.6	<.001
Arms	60	39	23.2	14.9	.01–.05
Legs	88	60	34.0	22.9	<.01

[1] P is the probability expressed as a decimal fraction of 1.000 that a difference in rate between the Placebo and Vitamin groups as great or greater would occur by pure chance of random selection.

the groups, when considered independently of other findings, would have limited significance. The findings on two other signs of vitamin A deficiency noted in the Study, follicular hyperkeratosis and conjunctival thickening (*see* below), were similar to that for dryness of hair. Taken with these other findings, the greater prevalence of dry hair, at the end of the Study year, in the Placebo than in the Vitamin group adds some support to the interpretation that there appeared to have been a therapeutic effect of the vitamin-mineral supplement.

Follicular hyperkeratosis also was significantly less frequent in the Vitamin than in the Placebo group at the second examination, the percentage of cases being 68 and 83, respectively. Table 3 shows that the prevalence of follicular hyperkeratosis was less in the Vitamin than in the Placebo group on each of four skin areas, and the difference in every area was either statistically significant or "highly significant."

An estimate was attempted in every subject of the amount and severity of follicular hyperkeratosis in terms of maximum area involved in any body region and maximum density (i.e., the number of hyperkeratotic follicles per unit area). These estimates were classified as slight, +, ++, and +++, and are only roughly quantitative.[8] Table 4 shows that not only was the prevalence of follicular hyperkeratosis less in the Vitamin than in the Placebo group, but also that among those in whom it occurred there was, in the Vitamin group, a tendency for a smaller skin area to be involved and for less dense involvement (*see* last column of Table 4).

The relative prevalence of pigmentation, protruding plugs, induration, and infection in our subjects provides a comparison with the follicular hyperkeratosis which has been proved to be a result of vitamin A deficiency. In the composite picture of the

[8] In the classification used, "slight" was a few scattered isolated papules, +++ a little less than that shown in the photographs of Frazier, Hu, and Chu (8).

pathological process given by Frazier, *et al.* and by Loewenthal, pigmentation is coincident with the first histopathological changes, and is the last sign to disappear in recovery. Protruding plugs come a little later, and they may become more numerous for a while during recovery, as the mouths of the dilated follicles shrink. Induration and infection are signs of advanced pathology, only a minority of follicles are so affected even in advanced cases, and these signs are the first to clear.

We should expect, therefore, if the follicular hyperkeratosis in our subjects was etiologically related to that described by Frazier and Hu and by Loewenthal, and if a therapeutic effect was op-

Table 4. Prevalence of cases of follicular hyperkeratosis at second examination classified according to extent of condition and according to density.

Rating of Cases	Number of Cases		Per Cent of Persons Examined		Ratio of Per Cent for Vitamin Group to Placebo Group
	Placebo Group	Vitamin Group	Placebo Group	Vitamin Group	
	MAXIMUM EXTENT IN ANY AREA				
Any Extent	215	178	83.0	67.9	0.82
Slight	89	95	34.4	36.3	1.06
+	48	33	18.5	12.6	0.68
++	36	23	13.9	8.8	0.63
+++	42	27	16.2	10.3	0.64
	MAXIMUM DENSITY IN ANY AREA				
Any Density	215	178	83.0	67.9	0.82
Slight	96	96	37.1	36.6	0.99
+	54	38	20.8	14.5	0.70
++	36	27	13.9	10.3	0.74
+++	29	17	11.2	6.5	0.58
Number Examined	259	262			

erative but still incomplete, that (a) in both the Vitamin and Placebo subjects in which the condition was found, nearly all would have pigmentation of the follicles and there would be no difference in this respect between the two groups; (b) the prevalence of protruding plugs would be less than of pigmented-follicles and the percentage might be nearly the same in both groups, because the number of protruding plugs would increase both during developing pathology and recovery; and (c) the prevalence of induration and infection would be less in both groups than of either of the two preceding signs, but there would be significantly less in the Vitamin than in the Placebo group. The findings summarized in Table 5 are, in general, in accord, with these predictions. The coincidence does not warrant any stress; it is indicative or suggestive.

Although the data (Tables 2 to 5) show that in the Vitamin group follicular hyperkeratosis was less frequent, less extensive and less severe than in the Placebo group, it is not proved that this difference represents a therapeutic effect of the vitamin supplement because there are no comparable data from the first examination. On the other hand, the evidence suggests that this

Table 5. Per cent of follicular hyperkeratosis cases in which various conditions were found.

Condition in Any Area	Number[1]		Per Cent of Cases		p[2]
	Placebo Group	Vitamin Group	Placebo Group	Vitamin Group	
Total Number of Cases	215	178	100.0	100.0	
Pigmentation Present	189	144	87.9	80.9	>.05
Protruding Plugs	92	87	42.8	48.9	>.10
Indurated	80	35	37.2	19.7	<.001
Infected	72	43	33.5	24.2	.02–.05

[1] The sum of the numbers of different conditions is greater than the total cases because many cases had more than one condition.
[2] Probability that percentages for Vitamin and Placebo groups would differ by the amount shown or more from chance.

was the case. As will be seen in the following tables, the two groups were not significantly different at the first examination with respect to the findings of any procedure used; their diets were alike; and their absenteeism during the first six months of the Study was approximately equal (3). At the end of the Study, in most of the other signs and clinical conditions, there was no difference between the two groups. The gross, clinical characteristics of the hyperkeratosis correspond, in the main, to those described by Frazier and Hu and others, although the distribution of lesions in our subjects differed. In their cases the hypertrophied follicles were most numerous on the limbs. The difference may be because most of our subjects wore belts and the constant mild irritation of the skin provoked the lesion most frequently on the back.

Attention must be drawn to the fact that 68 per cent of the Vitamin group had some degree of follicular hyperkeratosis after taking a supplement of 50,000 units of vitamin A five days a week for nine to twelve months (Table 4). In over half of these cases the condition was very slight and may justifiably be ignored. Hyperkeratosis of moderate extent (++ or +++) was present in 19 per cent of the Vitamin subjects compared with 30 per cent of the Placebo subjects, and for cases of moderate intensity the percentages were 17 and 25 per cent for Vitamin and Placebo subjects, respectively.

The following considerations may explain the persistence of follicular hyperkeratosis in a fairly large number of the Vitamin group, and also the small difference between it and the Placebo group at the end of the Study year. It is probable that not all cases of follicular hyperkeratosis are due to vitamin A deficiency, although many are (8). Many of the cases of Frazier, *et al.* and of Loewenthal were not completely cleared up after several months of therapy; and judging from their photographs and comments, those of our cases designated "slight" and probably

those designated + and ++ would have been considered by them as cured or practically cured. A much longer time than two to three months would have been necessary, judging by their descriptions, to have brought the cases of Frazier, *et al.* and of Loewenthal to a condition which would have met our criteria for "absent" follicular hyperkeratosis. Furthermore, their cases were in an advanced stage of severe and acute vitamin A deficiency, whereas our cases were affected by a relatively mild but probably chronic deficiency of long duration. The acute manifestations respond most quickly to therapy, for example, the prompt healing of keratomalacia; and the latest lesion to develop is the first to disappear. Kruse (32), in discussing the acute and chronic processes of deficiency diseases in relation to response to therapy, has stated that the chronic process which is slow in onset and progression is also slow in recession. This is in agreement with Straumfjord's (17, 18) finding that skin lesions were cured in some cases only after therapy for several years. A difference in the severity of vitamin A deficiency, and therefore in the rate of progression of lesions in China and Africa, may explain the difference in the amount of therapy and time required to clear up skin lesions in these countries (4-9, 13) and in the United States (10, 14-20). In the former countries, 10,000 to 25,000 units of vitamin A daily were used, and the cases were reported as cured, or nearly so, in two to three months; in the United States, 50,000 to 100,000 units daily were used, and the periods of therapy required ranged from six months to several years.

The findings in this section may be summarized as suggesting a therapeutic effect of the vitamin supplement in reducing the prevalence of dryness of hair and also the prevalence and severity of follicular hyperkeratosis. The data do not prove the point but, in view of the great need and paucity of reliable tests of mild nutritional deficiency states, they are sufficient to warrant

adequately controlled therapeutic tests of the suggestion they offer.

Vitamin A Deficiency: Conjunctival Conditions

The search for signs of early avitaminosis A in the conjunctiva appears to have been suggested by the long-established, specifically pathognomonic, ocular xerosis and keratomalacia in severe vitamin A deficiency in experimental animals and in children. Pillat (33) showed that this condition occurs in adults as well as in children. Blackfan and Wolbach (34) believed that early states of these pathological changes could be observed; and suggested that the presence of keratinized epithelial cells in scrapings from the cornea, nose, and mouth, or in secretions from the trachea, bronchi, kidneys, and vagina might serve as confirmatory diagnostic evidence in suspected cases of vitamin A deficiency. Sweet and K'Ang concurred in this view (13). They stated:

> "We believe that this (conjunctival scrapings) offers one of the most reliable methods of early diagnosis of avitaminosis A, though . . . . . no one procedure will suffice for all cases."

Nevertheless, Youmans, *et al.* (35) in a careful, critical study found that the evidence afforded by conjunctival smears was inadequate in the diagnosis of slight vitamin A deficiency in adults.

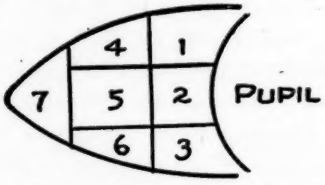
The subject was reopened by Kruse (36). He reported that it was possible to observe and measure with the biomicroscope certain changes in the conjunctiva which he interpreted as xerotic or pre-xerotic conditions resulting from chronic, mild vitamin A deficiency. He described these changes as varying degrees of opacity and thickening of the conjunctiva and elevated spots on it. Kruse reported that the opacity and thickening lessened and the spots diminished in size, one spot disappeared, after the daily ingestion of 100,000 units of vitamin A for eight months.

Kruse's work appeared shortly before our Study began. We

undertook, with his cooperation, to test his findings. A biomicroscopic examination of the conjunctiva was made on every subject on both the first and second examinations. Three observers carried out the first examination; two of these three, the second. The different observers checked each other frequently in the course of both examinations to ensure that their ratings were the same. The closeness of the ratings on the first and second examinations testified to the general uniformity of observation and scoring by the different observers on both examinations. However, the technique calls for subjective judging of translucency and opacity and there is inevitably some variation between examiners and for the same examiner in rating the degree of translucency or opacity and thickening.

On both examinations a record was made of the distribution of different degrees of opacity or translucency in each conjunctiva, the location of spots when present, their size, and whether or not they were elevated. Every person in both groups had some loss of transparency, most had opacity in some part of the conjunctiva at both examinations.

In order to permit statistical treatment of changes in transparency of the conjunctiva during the Study year, each of the conjunctival regions on the nasal and temporal sides of the pupil were divided into seven areas as follows:



There were thus twenty-eight areas, seven in each of four conjunctival regions.

The degrees of translucency observed were given the following scores: transparent 3; translucent, nearly transparent 2; trans-

lucent, nearly opaque 1; opaque 0. The conjunctival rating of each subject was simply the sum of the scores of the twenty-eight areas. It was impractical to attempt to grade degrees of opacity or degrees of thickening associated with opacity. Therefore, it is possible for some thinning of the conjunctiva to occur without affecting the score.

Table 6 summarizes the ratings in the Placebo and Vitamin groups on the first and second examinations. The mean ratings show that in both groups areas 1 + 3 had the highest scores, 4 +6 next, 2 + 5 and 7 had the lowest and were about equal.*

Table 6. Ratings on thickness of conjunctiva at first and second examinations on subjects in Placebo and Vitamin groups.

Conjunctival Area[1]	Placebo Group		Vitamin Group		Differences in Mean Ratings		
	Mean Rating	Standard Deviation	Mean Rating	Standard Deviation	Placebo Minus Vitamin	Standard Error	P
First Examination							
Whole Conjunctiva	36.49	7.16	36.04	7.95	+0.45	0.669	>.40
Area 1+3	13.78	2.62	13.72	3.11	+0.06	0.254	>.80
Area 2+5	8.03	3.44	7.68	3.34	+0.35	0.299	>.20
Area 4+6	10.76	2.42	10.70	2.74	+0.06	0.229	>.70
Area 7	3.92	0.50	3.94	0.69	−0.02	0.053	>.60
Second Examination							
Whole Conjunctiva	37.52	9.69	38.59	10.89	−1.07	0.911	>.20
Area 1+3	14.83	3.26	15.33	3.64	−0.50	0.305	>.10
Area 2+5	7.26	4.60	7.80	4.66	−0.54	0.409	>.10
Area 4+6	12.09	2.96	12.09	3.29	0	0.277	>.90
Area 7	3.34	1.33	3.36	1.30	−0.02	0.116	>.80
Number Examined	254		259				

[1] See text, page 116.

*The scores of the paired areas 1 + 3, 2 + 5, 4 + 6 are the *sum* of the eight ratings, of area 7 of only four ratings. Accordingly, to compare the scores in area 7 with those of the paired areas, they should be multiplied by 2.

The scores are directly proportional to the degree of transparency, or inversely proportional to the degree of opacity.

On the first examination the Placebo group had slightly higher scores in all areas, except 7, where the two groups were nearly identical. None of the differences are statistically significant.

On the second examination the scores for the Vitamin group were higher than for the Placebo group in every area except 4 + 6, where the two were identical. None of the differences of the mean ratings are statistically significant, though the values of P (the probability of a difference as great or greater occurring by chance) are lower in the cases of areas 1 +3 and 2 + 5 than any in the first examination.

Since the Placebo group had the higher score on the first examination and the Vitamin group on the second, there was a difference between the groups in the amount of change during the year. The statistical significance of this reversal in the relation of the two groups can be appraised by tabulating the changes in score for each individual between the first and second examination, and then computing the mean change and the variance in the usual manner. In this analysis of individual

Table 7. Changes in conjunctival ratings for individual subjects between first and second examinations (second rating minus first rating).

Conjunctival Area[1]	Placebo Group		Vitamin Group		Placebo Mean Minus Vitamin Mean		
	Mean of Differences	Standard Error	Mean of Differences	Standard Error	Difference	Standard Error	P
Whole Conjunctiva	+1.028	0.502	+2.556	0.483	−1.528	0.696	.02–.05
Area 1+3	+1.057	0.211	+1.612	0.189	−0.555	0.283	.05
Area 2+5	−0.776	0.190	+0.127	0.181	−0.903	0.262	<.001
Area 4+6	+1.323	0.204	+1.396	0.196	−0.073	0.282	>.70
Area 7	−0.577	0.076	−0.579	0.081	+0.002	0.111	>.90

[1]See text, page 116.

change, the effect of variations in measurements and rating criteria between the first and second examination is constant for the two groups and the significance of any difference in change for the two groups is measured.

The data on change in ratings is summarized in Table 7. The mean change per person for all twenty-eight conjunctival areas between examinations for the Placebo group was +1.028 and for the Vitamin group + 2.556 which indicates that a greater improvement occurred in the Vitamin than in the Placebo group. The difference in degree of improvement between the two groups is statistically significant.

A greater change in ratings for transparency for the Vitamin subjects is not found for all conjunctival areas. In area 7 and in area 4 + 6, there is very little difference in the average change between examinations for the Vitamin and Placebo subjects. Ratings for area 7 were lower and those for area 4 + 6 were higher at second examination for both groups. In area 1 + 3, both groups had improved ratings, but there was greater improvement for the Vitamin subjects and the difference has borderline significance statistically (P is .05). The greatest difference in change for the two groups is found for area 2 + 5 and the difference is statistically very significant.

The change in ratings for area 2 + 5 needs special comment. There was only a very slight and not a statistically significant improvement in the average rating at second examination for the Vitamin subjects. Superiority for the Vitamin group arises from the fact that the Placebo group had a significantly lower average rating at the second examination than at the first examination. This apparently suggests that in area 2 + 5 the conjunctivae of Placebo subjects became worse during the Study year, whereas the conjunctivae of Vitamin subjects remained essentially unchanged. This may have occurred. Area 2 + 5 is where the greatest thickening is found and area 2 frequently was occupied

by elevated opaque spots which did not disappear from the conjunctivae of subjects in either group (Tables 8 and 9). Furthermore, any progression of the conjunctival lesion would be expected to affect the degree of opacity in this area, the horizontal meridian. On the other hand, the possibility that there was some shift in standards for judging opacity or degree of translucency between the first and second examinations must be borne in mind. Any change in standards would affect ratings for both the Vitamin and Placebo subjects, and the general conclusion remains that the comparative change in ratings indicates some superiority for the Vitamin subjects.

Kruse reported that the changes in the conjunctiva with vitamin A therapy appeared first and were greatest in areas 1, 3, 4, and 5 and that, in the beginning, negligible changes, if any, occurred in areas 6 and 7. Our findings confirm those of Kruse to the extent that, using his criteria, some improvement occurred following extensive, massive vitamin A therapy in approximately the same areas as he reported.

In each of the Study groups there were some persons who showed a fairly consistent general improvement in both eyes, although it is apparent from the small average change per person

Table 8. Distribution of subjects at first and second examinations according to number of elevated conjunctival spots on both eyes.

Examination and Group	Number of Subjects	Percentage With Specified Number of Elevated Conjunctival Spots					
		Total	None	1	2	3	4
First Examination							
Placebo Group	254	100.0	20.1	15.8	33.5	16.9	13.8
Vitamin Group	259	100.0	18.1	18.5	40.2	10.8	12.4
Second Examination							
Placebo Group	254	100.0	20.1	14.6	33.1	19.7	12.6
Vitamin Group	259	100.0	20.5	17.8	38.6	10.0	13.1

in the total score for the 28 areas that few subjects, even in the Vitamin group, received a higher rating for all or for most of the areas. As already mentioned, ratings for the four areas numbered 7 were usually lower at second examination and it frequently happened that the same person had higher ratings for several areas and lower ratings for other areas. In order to estimate the numbers of persons in each group who showed the most definite and general improvement, a count was made of those who had some increase in the total score for each of the paired areas 1 + 3, 2 + 5, and 4 + 6. Not all of the eight areas included in each of the three totals showed any improvement, but one or more did, and the net total score for each of the three groups of eight areas was higher at the second examination. Among the Vitamin subjects, fifty-nine persons or 23 per cent had this general improvement in transparency, and among Placebo subjects thirty-three or 13 per cent, had a similar change. The difference between the groups is statistically very significant. These selected subjects were not the only ones who had definite improvement in some areas, but they are the ones with the most extensive conjunctival improvement, and a larger percentage of the Vitamin than of the Placebo group showed this general improvement.

Table 9. Change in number of elevated conjunctival spots between first and second examination for individual subjects.

Difference in Number of Spots (2nd Minus 1st Examination)	Placebo Group	Vitamin Group
Total Subjects	100.0	100.0
+3 Spots	1.6	0.4
+2 Spots	3.5	4.2
+1 Spot	14.2	15.4
No Change	59.8	56.4
−1 Spot	17.7	19.3
−2 Spots	2.8	3.9
−3 Spots	0.4	0.4
Number of Subjects	254	259

The superiority in the change for the Vitamin subjects is less than might be expected from Kruse's report (36). Several considerations may be relevant to an evaluation of the relatively

small improvement of subjects on therapy in this Study. The amount of vitamin A given was one-half that administered by Kruse, 50,000 as compared to 100,000 I.U. daily, and the average number of days of therapy for our subjects was about equal to the therapy period on which Kruse has reported. It is unknown whether this difference in dosage would have any effect on the rate of recession. Kruse examined forty-seven, or about one-half his male cases, for skin lesions and noted only occasional indefinite lesions among the "spot" cases and none in persons with less severe conjunctival lesions, whereas the majority of our subjects had some degree of follicular hyperkeratosis. If, as Kruse has suggested, skin lesions are a later, more advanced manifestation of vitamin A deficiency, our subjects had more severe, chronic deficiency than did the cases studied by Kruse, and the skin lesions might be expected to respond to therapy more quickly than the eye lesions. Results of the eye examinations at the first examination also indicate a higher prevalence of advanced conjunctival changes in our subjects than in Kruse's group; in only 2 per cent of our group was the conjunctival lesion limited to marked translucency compared with 13 per cent in Kruse's group with a similar minimal change. After eight months of therapy, Kruse reported one spot case and eight less severe cases cured, but in a later note (37) he states that "for the severe cases at least two years will be required from the beginning of therapy to complete recession."

The observations and conclusions of Kruse were challenged by Callison (38). She reported that in human subjects on an experimental vitamin A deficient diet, there were no detectable changes in the conjunctiva or cornea either when the dark adaptation became impaired, or when it was restored by adequate vitamin A therapy.

Kruse (39) replied that the ophthalmologists who made the examinations on Callison's subjects did not use his criteria, that

his work was published two years later, and that they were looking for keratinization, whereas the conditions he described were varying degrees of xerosis and pre-xerosis.

The last point was questioned by Berliner (40), who affirmed that the conditions described by Kruse as indicative of mild, but chronic, vitamin A deficiency, are merely pre-senile and senile alterations of the conjunctiva which bear no relation to vitamin A deficiency; that they occur in people with normal blood vitamin A levels; that neither the thickness nor the translucency of the conjunctival epithelium can be measured by Kruse's technique; and, perhaps his most serious criticism, that the conditions Kruse described are in the subepithelial structures which are not affected by vitamin A deficiency, and are not epithelial changes which alone are pathognomonic of avitaminosis A.

These criticisms by Berliner were answered by Kruse (37). He again emphasized that the subepithelium, as well as the epithelium, is involved in conjunctival manifestations of vitamin A deficiency, and stated that the so-called senile changes are really the manifestations of chronic deficiencies in which time and not senility *per se* is the essential point.

The only reports we have found of prolonged therapeutic trial of Kruse's findings are those of Jolliffe and Stern (41) and of Getz (42). Jolliffe and Stern found that of ten subjects given 50,000 units of vitamin A twice daily by mouth for ten months, seven showed evidence of responding in the manner described by Kruse. In two cases, elevated spots disappeared and in the other five the color of the outer segments of the sclera changed from a slightly yellow or cream color to blue, the epithelium became thinner so that the deeper scleral vessels became visible; and the spots became less elevated. As there were no placebo controls in this series, these findings are not conclusive.

Getz took very large amounts of vitamin A for thirty-five weeks and then subsisted for one and one-half years on a diet

providing less than 500 I.U. vitamin A daily. After the third month on the vitamin A deficient diet, the progression of conjunctival changes described by Kruse appeared. These findings only confirmed the gross changes described by Pillat (33); Pillat also described the course of their rapid disappearance with moderate vitamin A therapy (10,000 I.U. daily). Neither the findings of Getz nor those of Pillat bear directly on the question at issue here, which is whether or not the opacity and thickening seen in nearly all adults on diets which often would be considered adequate in vitamin A, disappear after many months' ingestion of large amounts of vitamin A. A second and related question is whether or not opacity and thickening of the conjunctiva are always, or often, a consequence of low vitamin A intake.

The data obtained in this Study do not answer these questions. The Vitamin group became "significantly" better than the Placebo group, but the degree of improvement was very small. The result is suggestive that a slight therapeutic effect occurred and to this extent it tends to support the work of Kruse.

Vitamin A Deficiency: Elevated Conjunctival Spots

As stated above, according to Kruse, in chronic vitamin A deficiency, the conjunctiva becomes thickened leading eventually to the formation of opaque elevated areas or spots. These are usually confined to the horizontal meridian, extending laterally a varying distance from just outside the limbus. Apart from pterygia, which overlap the corneo-scleral margin, Kruse made no distinction between different types of spots.

One category of conjunctival spots are Bitot's spots, whose appearance in severe vitamin A deficiency is well known. They are described as appearing first as foam-like dots or slender short lines which can be scraped away; but they reform quickly. Gradually the dots become larger and coalesce into pearly or silvery spots or plaques. On the temporal side of the cornea they

are usually triangular; they may be round or oval; on the nasal side they usually remain as small dots (8, 33, 40, 43, 44). On adequate vitamin A therapy, spots which were observed to have been formed in this way disintegrate into dots, and then disappear with the coincident repair of the keratinization and xerosis of the conjunctiva.

Nicholls and Nimalasuriya (43) were of the opinion that the foamy dots indicate acute, severe vitamin A deficiency, and the more solid patches a reaction of the conjunctiva to chronic vitamin A deficiency. Metivier (44) concurred in this view, but reported observing cases of more chronic (and presumably mild) deficiency where there were no spots, and also other conjunctival spots in children and in a few adults which were not changed by vitamin A therapy. Metivier concluded that in some cases Bitot's spots are a diagnostic sign of vitamin A deficiency and in others they have no morbidity significance. Metivier stated that he has seen in Trinidad no Bitot's spots in adults over 21, with one exception.

On the first examination the presence or absence of elevated conjunctival spots was noted and their location, when they occurred. A distinction was made between elevated and non-elevated spots. The latter were included in the data of the preceding section as opaque areas. This section deals only with the elevated spots.

Approximately 80 per cent of the subjects in both the Placebo and Vitamin groups had, on the first examination, one or more elevated conjunctival spots (Table 8). The distribution of subjects with one, two, three, or four spots was also nearly the same in both groups.

On the second examination the picture was essentially unchanged, both with respect to the number of subjects with elevated spots and their distribution according to the number of spots (Table 9). There was no difference in this respect be-

tween the Placebo and Vitamin groups. The differences noted between the first and second examinations express in most cases a difference in judgment in the two examinations on whether or not the spots were elevated; there were probably very few cases in which spots really changed from elevated to nonelevated.

We failed, therefore, to observe in our subjects the reduction in elevated conjunctival spots under vitamin A therapy reported by Kruse (36) or by Jolliffe and Stern (41). Our findings are in accord with those of Metivier (44) except that they go much further, in that few if any of our subjects responded to massive vitamin A therapy given five days a week for nine to twelve months. None of the spots we observed were the pearly or silvery concretions, nor the earlier stage of foamy dots characteristic of the Bitot's spots in cases of proved vitamin A deficiency. Yet we feel it is premature to conclude that conjunctival spots, occurring in subjects such as ours, are as Berliner (40) contends, pre-senile and not xerotic (i.e., not the result of vitamin A deficiency). The use of the term "pre-senile" here is a conclusion made *faute de mieux* in the absence of a proved etiology. Study is needed of the question whether or not these spots are irreversible changes of earlier vitamin A deficiency, and whether or not they can be prevented by habitual intakes of much larger amounts of vitamin A than are at present considered "adequate." Our study provides no data on these questions.

Pett (45) has reported findings which are in the same direction as ours after trial of a supplement of 10,000 I.U. vitamin A for ten weeks.

Thiamin Deficiency: Abnormalities in Reflexes, Calf Muscle Tenderness, and Plantar Dysesthesia

Many of the signs of thiamin deficiency are those of peripheral neuropathy. Among them are disturbance in and absence of ankle and knee jerks, plantar dysesthesia, calf muscle tenderness,

and impaired vibratory sensibility in the toes. According to Holt and Najjar (46), loss of ankle reflexes, motor weakness, ataxia, and muscular hyperesthesia (on squeezing) precede loss of vibration, position and temperature sense. Stern, Wortis, and Jolliffe place loss of vibratory sensibility prior to loss of ankle jerks (47).

None of these signs associated with thiamin deficiency are specifically pathognomonic. It is hazardous to make a diagnosis, even when they are present, unless there is some factor known to predispose a subject to thiamin deficiency, or there is definite laboratory evidence (low urinary thiamin or high blood pyruvate).

Abnormal neurological signs are found surprisingly often in an apparently healthy population, and were found in the subjects of this Study (2). It is important to ascertain, if possible, in what proportion of such subjects these signs indicate thiamin deficiency. To answer this question, other evidence is necessary; such evidence is furnished by a therapeutic test.

Signs of peripheral neuropathy were sought in our subjects at the beginning and end of the Study. Subjects in the Vitamin group received 10 mgs. of thiamin daily. A positive response to the therapeutic test would consist in finding that the signs had disappeared in some of the Vitamin group, in those cases in whom the cause was thiamin deficiency, whereas they persisted in the Placebo group to the end of the Study year with a resulting lower frequency at the end of the year in the Vitamin than in the Placebo group.

Findings in the two examinations on absent reflexes, calf muscle tenderness, and plantar dysesthesia are summarized in Table 10. Many more cases with these abnormalities were noted at the second examination than at the first. This difference almost certainly is to be ascribed to the difference in observers and technique used at the two examinations. The neurological examinations were made by two observers on the first examination,

by another observer on the second examination. Nevertheless, there is this much agreement, that neither at the first nor the second examination was there a significant difference in the frequency of signs of neuropathology between the Placebo and Vitamin groups.

Table 10. Prevalence of neurological abnormalities at first and second examinations in Placebo and Vitamin groups.

Condition	Number of Cases				Per Cent of Total Examined			
	First Examination		Second Examination		First Examination		Second Examination	
	Placebo	Vitamin	Placebo	Vitamin	Placebo	Vitamin	Placebo	Vitamin
Number Examined	255	258	260	257	100.0	100.0	100.0	100.0
Reflexes:								
Ankle Jerk								
One Absent	1	0	10	7	0.4	0	3.8	2.7
Both Absent	3	5	16	14	1.2	1.9	6.2	5.4
Knee Jerk								
One Absent	0	0	8	5	0	0	3.1	1.9
Both Absent	1	0	9	9	0.4	0	3.5	3.5
Persons With One or More Ankle or Knee Jerks Absent	4	5	34	29	1.6	1.9	13.1	11.3
Biceps Jerk								
One Absent	0	0	14	12	0	0	5.4	4.7
Both Absent	0	0	10	9	0	0	3.9	3.5
Triceps Jerk								
One Absent	0	0	7	7	0	0	2.7	2.7
Both Absent	0	0	14	11	0	0	5.4	4.3
One or More of Four Reflexes Absent	4	5	51	49	1.6	1.9	19.6	19.1
Other Neurological:								
Calf Muscle Tenderness	0	1	48	56	0	0.4	18.5	21.8
Plantar Dysesthesia	39	38	94	114	15.3	14.7	36.2	44.4
Persons With One or More of Tenderness or Dysesthesia	39	39	121	136	15.3	15.1	46.5	52.9

Some may doubt the reliability of the high prevalence of calf muscle tenderness and plantar dysesthesia noted in both groups at the second examination. A check on the order of magnitude of these figures was provided by the paresthesias evoked by the stimulus of an electrically driven vibrator used for determining thresholds to vibratory sensibility (*see* below). The stimulus was much milder than was used in stroking the sole of the foot to test for plantar dysesthesia. It consisted of a vibrating stylus 0.08 inches in diameter, applied to the dorsum of the toe. The observations were made by another observer who was unaware of the findings of the physical examination. He recorded whenever a subject told him that he felt any unusual sensations; the most frequent of these were burning or stinging when the vibratory stimulus was applied. The subjects certainly did not expect to perceive burning or stinging in this test. These sensations were reported by 27.1 and 28.5 per cent of the Placebo and Vitamin group subjects, respectively (Table 15). This instrument provides a far more reliable and more uniform method of testing for paresthesia, which is a sign of neuropathy, than stroking the sole of the foot.

In view of the negative result of the therapeutic test, i. e., no difference between the Vitamin and Placebo groups at the second examination, it is highly probable that the high prevalence of absent reflexes, calf muscle tenderness, and plantar dysesthesia in our subjects (most of them men under 30 years of age) was unrelated to any existing thiamin deficiency.

The origin and etiological significance of the above signs in subjects such as ours are unknown at present.

Thiamin Deficiency: Loss of Vibratory Sensibility in the Toes

Nutritional deficiency disease is one of a number of causes of peripheral neuropathy resulting in impaired vibratory sensibility.

The latter condition occurs in severe thiamin deficiency following impairment of motor function (46); and it is repaired with adequate therapy (48, 49). On the other hand, it is frequently found in subjects who have few, or no other, signs of peripheral neuropathy and no obvious dietary deficiency.

A high prevalence of impaired vibratory sensibility was found in the first examination of our subjects. Of 1,153 men, nine, or 0.8 per cent, had loss of vibratory sensation in the toes to the tuning fork C-128 (128 C.P.S.); and of 996 men tested, 25.7 per cent did not perceive the vibrations of the C-256 tuning fork (256 C.P.S.).

In the report of the first examination (2) this comment was made:

> "The results of the re-examination may indicate to what extent impaired vibration sensation in the toes can be repaired in young adults by large vitamin supplements, taken for approximately a year."

In order to test this possibility thoroughly, a more sensitive and more quantitative method of measuring vibratory sensibility was devised. Accordingly, at the second examination the men's toes were tested with both the 128 C.P.S. and 256 C.P.S. tuning forks and with an electrically driven vibrator. With this apparatus it was possible to measure thresholds of vibratory sensibility over a wide range of frequency. Details of the apparatus and the method of using it have been described (50).

The Placebo and Vitamin groups in this section are essentially the same as the groups referred to in the rest of the report, except as follows: Not all of the men could be tested and some men were removed from the comparisons of thresholds of vibratory sensibility because the results of their tests were judged to be unreliable. No men have been included who did not receive the vitamin or placebo supplement regularly. In those cases in which the responses to the 256 C.P.S. tuning fork were not positive for

every toe, the foot with the fewer positive responses was selected for testing with the electrical vibrator. At the time of testing, the operator did not know to which group a man belonged. The subjects were tested with their eyes closed.

In Table 11 are shown the results of testing 425 men on four toes of one foot with the two tuning forks. All but two of the men gave positive responses on all four toes to tuning fork 128 C.P.S. This is essentially the same result obtained at the first examination, when nine men out of 1,153 showed loss of sensation to this tuning fork.

There were many negative responses to the 256 C.P.S. tuning fork. Of 425 men, 42 per cent had one or more toes which were unresponsive. At the first examination the percentage with absent vibration sensation to this tuning fork was only 26. The discrepancy can be explained by the more careful attention paid to this test at the second examination when four toes on each

Table 11. Response of Placebo and Vitamin subjects to 128 C.P.S. tuning fork and to 256 C.P.S. tuning fork at second examination.

Group	Number of Men Tested	Four Toes Positive		Negative, 1–4 Toes	
		Number	Per Cent	Number	Per Cent
	128 C.P.S. TUNING FORK				
Total	425	423	99.5	2	0.5
Placebo Group	195	195	100.0	0	0
Vitamin Group	230	228	99.1	2	0.9
	256 C.P.S. TUNING FORK				
Total	425	247	58.1	178	41.9
Placebo Group	195	120	61.5	75	38.5
Vitamin Group	230	127	55.2	103	44.8

person were tested routinely. If all the toes had been tested at the first examination it is possible that some men classified as positive would have given a negative response on one or more toes.

Table 12 is presented to show the effect of omitting the test for some toes. It shows the number of toes which were positive. All the men, 613, who were tested at the second examination with the 256 C.P.S. tuning fork are included, regardless of amount of therapy received. It can be seen that if only those men with negative responses on two or more toes were considered as negative, there would be 160 men (76 + 40 + 44), or 26.1 per cent, in this class, which is similar to the proportion 25.7 per cent found negative at the first examination by a less exhaustive procedure.

There is nothing in Tables 11 and 12 to show any positive effect of the vitamin supplementation. The Vitamin group was slightly but not significantly worse than the Placebo group. A reliable comparison of the responses of the same person at the two examinations cannot be made because the procedure in the two tests was not uniform.

Data on thresholds of vibratory sensibility at different frequencies, obtained with the electrically driven vibrator, are collected in Table 13. The thresholds are given in arbitarary units which are based on readings from the voltmeter on the instrument. The possible range in threshold was from 1 to 7, and the smaller the number the lower the threshold or strength of stimulus required

Table 12. Response to 256 C.P.S. tuning fork at second examination. Distribution of men according to number of toes positive.

Group	Number of Men Tested	Number of Toes Positive[1]				
		4	3	2	1	0
Total	613	352	101	76	40	44
Placebo Group	302	179	51	37	19	16
Vitamin Group	311	173	50	39	21	28

[1] Number of men with fewer than 3 toes positive = 160, 26.1 per cent.

(50). Some persons gave no response to the maximum stimulus used. Results were taken from the foot which was chosen as previously explained, and the results from the most sensitive toe on this foot have been used. All the readings so obtained at one frequency have been averaged, and the mean thresholds are shown in Table 13. Not all persons were tested at every frequency. The subjects are divided into three age groups, as the threshold to vibratory sensibility rises with age (50,51).

The differences between the Placebo and Vitamin groups are small in all age groups and at all frequencies, and none are statistically significant. The differences are not even all in the same direction. There are 25 comparisons in the three age groups between the Placebo and Vitamin groups. In 11 of these the mean thresholds for the Vitamin group are higher, in 7 they are equal, and in 7 they are lower.

Table 13. Mean vibration thresholds at various frequencies. Comparison of Vitamin and Placebo groups at different ages.[1]

Age Group in Years and Study Group	Mean Threshold[2] at Specified Frequency, Cycles Per Second									
	50	100	200	250	300	350	400	500	600	800
All Ages										
Placebo Group	3.8	2.5	3.1	3.8	4.3	5.4	5.0	5.6	6.0	6.2
Vitamin Group	3.9	2.7	3.2	3.9	4.4	5.5	5.1	5.6	6.0	6.3
20–29 Years										
Placebo Group	3.6	2.3	2.9	3.6	4.1	5.3	4.9	5.6	5.9	6.2
Vitamin Group	3.8	2.5	2.9	3.7	4.2	5.5	5.0	5.5	5.9	6.3
30–39 Years										
Placebo Group	4.0	2.8	3.5	4.2	4.6	5.4	5.1	5.8	6.1	6.3
Vitamin Group	3.9	2.8	3.4	4.1	4.6	5.6	5.4	5.7	6.1	6.3
40 Years or More										
Placebo Group	4.3	3.3	4.2	4.9	5.1	*	*	*		
Vitamin Group	4.5	3.5	3.8	4.6	5.1	5.7	5.6	6.1		

* Fewer than ten cases.
[1] None of the differences are statistically significant.
[2] Threshold measured in arbitrary units from voltmeter.

It was possible that the choice of the most sensitive toe for the comparison of thresholds obscured differences between the two

Table 14. Percentage distribution of subjects according to threshold of vibratory sensibility in toes at two frequencies and for two age groups.

Threshold	Frequency of 250 C.P.S.				Frequency of 400 C.P.S.			
	19–29 Years		30 Years and Over		19–29 Years		30 Years and Over	
	Placebo	Vitamin	Placebo	Vitamin	Placebo	Vitamin	Placebo	Vitamin
	Toe 1—large toe							
Total	100	100	100	100	100	100	100	100
1	0	1	0	0	0	0	0	0
2	5	5	0	2	0	0	0	0
3	16	14	11	10	1	4	0	1
4	36	32	18	20	11	9	7	7
5	27	30	34	35	24	21	23	16
6	12	10	28	18	34	33	18	24
7	1	4	3	6	8	11	10	11
No Response	3	4	5	9	22	23	43	41
	Toe 4							
Total	100	100	100	100	100	100	100	100
1	2	3	0	0	0	1	0	0
2	7	8	3	3	0	1	0	0
3	27	21	16	17	5	6	2	2
4	33	33	21	27	13	8	10	8
5	25	26	31	35	43	38	31	27
6	3	5	21	12	24	25	21	25
7	1	2	5	1	4	6	5	7
No Response	2	2	2	4	12	15	31	31
Number of Subjects	136	141	61[1]	89[2]	136	141	61	89

[1] Includes 9 persons aged 40 years or older.
[2] Includes 17 persons aged 40 years or older.

groups, because the most sensitive toe may have the maximum sensibility attainable. Therefore, data on the distribution of thresholds for two toes, toe 1 (the large toe) and toe 4 (that next to the little toe) to two frequencies, 250 and 400 C.P.S., are presented in Table 14. The data are given for two age groups, 19-29 years inclusive and 30 years or over. These data again show no significant differences between the Placebo and Vitamin groups. They also show that the thresholds tended to be lower for toe 4 than for toe 1, i.e., the sensibility was greater in toe 4. There was a decrease in sensibility with age in both toes at both frequencies.

Many subjects reported perceiving a burning or stinging sensation when the vibrating stylus was applied. Often a subject felt a number of, to him, unexpected sensations of burning, stinging, and tickling, one or all of which spread to the sole or up the leg, sometimes one or two seconds after the vibrating stimulus was withdrawn. In Table 15 are collected the data on reports of burning or stinging; these paresthesias were the most frequent and were described most clearly.

There was no significant difference in the frequency of paresthesias in the Placebo and Vitamin groups. Paresthesias were more frequent in those whose perception of vibration was so impaired that their thresholds could not be measured (unreliable responses) than in those in whom it could be measured (reliable responses); and they were more frequent in the older age group, for which higher thresholds also were obtained (Table 14).

It was interesting to examine if this apparent association of lower vibratory sensibility and tendency to paresthesias would persist through a more detailed analysis of the data. Accordingly, the subjects in the combined Placebo and Vitamin groups were separated into those without and those with paresthesias. For two age groups, 19-29 years and 30 years and over, the distributions of thresholds in toe 1 and toe 4 at 250 and 400 C.P.S. are compared in Table 16 for persons without and with pares-

Age and Study Group	Subjects Giving Reliable Responses to Vibratory Stimulation			Subjects Giving Unreliable Responses to Vibratory Stimulation			All Subjects		
	Total	Paresthesia		Total	Paresthesia		Total	Paresthesia	
		Absent	Present		Absent	Present		Absent	Present
	PER CENT OF GROUP TOTAL								
19–29 Years									
Placebo	100.0	80.1	19.9	100.0	58.3	41.7	100.0	78.4	21.6
Vitamin	100.0	78.7	21.3	100.0	12.5	87.5	100.0	75.2	24.8
30 Years or More									
Placebo	100.0	63.9	36.1	100.0	50.0	50.0	100.0	61.6	38.3
Vitamin	100.0	68.5	31.5	100.0	37.5	62.5	100.0	66.0	34.0
	NUMBER OF CASES								
19–29 Years									
Placebo	136	109	27	12	7	5	148	116	32
Vitamin	141	111	30	8	1	7	149	112	37
30 Years or More									
Placebo	61	39	22	12	6	6	73	45	28
Vitamin	89	61	28	8	3	5	97	64	33

Table 15. Frequency of paresthesia (burning or stinging) on vibratory stimulation in Placebo and Vitamin groups.

thesias. The data used were only from those subjects who gave reliable responses. In the younger age group thresholds tended to be lower, i.e., sensibility was higher, in the subjects who did not have paresthesias. The difference between those who did and those who did not have paresthesias was in the same direction but less in the older age group in toe 1, but there was practically no difference in toe 4. This is a reasonable result because as sensi-

Threshold	Frequency of 250 C.P.S.				Frequency of 400 C.P.S.			
	19–29 Years		30 Years or More		19–29 Years		30 Years or More	
	Paresthesia Absent	Paresthesia Present	Paresthesia Absent	Paresthesia Present	Paresthesia Absent	Paresthesia Present	Paresthesia Absent	Paresthesia Present
	Toe 1—Large Toe							
Total	100	100	100	100	100	100	100	100
1	1	0	0	0	0	0	0	0
2	6	0	2	0	0	0	0	0
3	15	14	13	6	3	0	0	2
4	37	23	18	22	12	2	9	2
5	27	33	37	30	25	14	21	14
6	9	19	20	26	33	35	21	22
7	2	4	4	6	8	16	10	12
No Response	2	7	6	10	20	33	39	48
	Toe 4							
Total	100	100	100	100	100	100	100	100
1	3	0	0	0	0.5	0	0	0
2	8	4	4	2	1	0	0	0
3	27	14	15	20	7	0	2	2
4	32	35	30	14	11	5	9	8
5	24	32	29	42	41	35	30	26
6	3	7	16	16	24	26	25	20
7	0.5	5	2	4	4	9	4	10
No Response	2	4	4	2	10	25	30	34
Number of Subjects	220	57	100	50	220	57	100	50

Table 16. Percentage distribution of thresholds of vibratory sensibility in toes at two frequencies and in two age groups with and without paresthesia on vibratory stimulation. Placebo and Vitamin groups are combined, and only persons with reliable perception of vibratory stimulation are included.

bility diminishes the range within which differences could be measured becomes narrower. The differences in threshold be-

tween those with and without paresthesias would have been larger, in both age groups, if subjects who gave unreliable responses had been included (*see* Table 15). The unreliability of response was itself an indication of impaired sensibility; the thresholds, whatever they were, were high and the frequency of paresthesias was very high.

It is clear from the foregoing that vibratory sensibility diminishes with age and sensory function also becomes impaired (*viz.*, the increase in paresthesias). The vitamin supplement taken for nine to twelve months did not noticeably affect these degenerative processes. The answer to the question raised in the report of the first examination (2), whether impaired vibratory sensibility "can be repaired in young adults by large vitamin supplements taken for approximately a year," is conclusive: it cannot. However, the limitations of our data call for two qualifications: one, the "young adults" referred to are those who would be considered healthy by the usual criteria; and two, the conclusion is valid only for the vitamin supplements used in this Study and for the specific period of therapy. The effects of pyridoxin, pantothenic acid, biotin, folic acid, and other members of the vitamin B complex were not tested here, and their effects cannot be predicted. They need to be tested because the phenomenon which can be measured and experimented with here is one of great importance. It is the aging process.

Riboflavin Deficiency: Corneal Vascularization

According to Kruse, *et al.* (52), one of the surest signs of riboflavin deficiency in man is a vascularizing keratitis of the limbus and cornea. Fine capillaries situated just under the epithelium arise from the apices of the marginal loops in the limbal conjunctiva and anastomose to form a series of loops which extend centripetally. Sydenstricker, *et al.* (53) stated:

"At the present time (1941) it seems that superficial vascular

> keratitis is the earliest and most common visible manifestation of riboflavin deficiency as well as a reliable index of early deficiency of the B group of vitamins."

Tisdall, *et al.* (54), Gregory (55), Fish (56), and Mann (57) have commented on the ambiguity and inconsistencies in the descriptions given by Kruse and Sydenstricker on the precise location of a pathognomonic increase in corneal vascularity.

There is also an observational difficulty in deciding whether the tips of the vessels are in the limbus or in the cornea when the capillaries do not extend far on to the cornea. The limbus or corneo-scleral junction is histologically a wedge-shaped zone, in which the upper scleral layer overlaps the border of insertion of the lower corneal layer. Consequently, vessels in the sclera may appear through the biomicroscope to be in the outer margin of the cornea.

According to Sydenstricker, the earliest microscopic sign of ariboflavinosis is a marked increase in the number and size of vessels comprising the limbal plexus. It is possible to infer from some of the writings of Kruse and Sydenstricker, without being certain, that any vascularity of the limbus is pathological and indicative of ariboflavinosis, although Sydenstricker's latest reports (58,59) indicate modification of this view.

On the other hand, according to Mann:

> "It would seem unwise to include the full limbus among the signs of riboflavin deficiency, the earliest sign of which should be taken to be a budding out of new capillaries from the limbal loops at their apices, with extension on to the true cornea. This should be present in both eyes and around the whole corneal circumference, although it may vary in depth in the two eyes. Even then the final certainty must be emptying of the new loops after administration of riboflavin."

Gregory and Fish are in accord with this view, that it is normal for vessels to occupy the whole width of the limbus.

The point at issue is important because, in general, those who consider pre-corneal congestion, i.e., visible capillaries not necessarily extending beyond the limbus, as pathognomonic have reported a high incidence of ariboflavinosis, 30 to 100 per cent, in otherwise normal population groups, whereas those who used criteria such as set out by Mann above report a low incidence ranging from 1.5 to 6.5 per cent.

There is also disagreement between Kruse and Sydenstricker, on the one hand, and most other observers on the other, whether or not limbal and corneal vessels may be caused to disappear entirely, i.e., are completely absorbed, or merely to empty with riboflavin therapy.

The extreme position in this controversy is taken by Vail and Ascher (60) who state that they have seen entrance of newly formed capillaries into corneal tissue proper only in cases of corneal disease and injury and not in ariboflavinosis. They are convinced that, except in such corneal disease, the condition described as corneal vascularization is merely an engorgement of pre-existing limbal plexus. They conclude from their anatomical studies that the situation of the concentric collaterals and limbal capillary loops in the cornea proper is only apparent and not real; that these actually are situated in the semi-transparent scleroconjunctival limbal zone which is continuous with the opaque bulbar coat. The illusion of its vessels penetrating the cornea arises from its overlapping the corneal rim.

Vail and Ascher found no correlation between dietary habits and the frequency of vascular congestion in the limbal region. The number of positive cases was higher in a good-diet group than in a poor-diet group.

Our Study began before the reports criticizing the observations of Kruse and Sydenstricker on the relation between corneal vascularity and ariboflavinosis had appeared. A biomicroscopic examination of the cornea under slit-lamp illumination was made

on every subject at both the first and second examinations. Loops or arcades of vessels which appeared to be situated central to the limbus were recorded on a drawing of the cornea and located according to hours of the clock. The number of arcades in each series of loops was noted. In the second examination the distance from the limbus to the central end of the loops was measured with a micrometer eye-piece.

Table 17. Distribution of total number of hours of arcades (both eyes) of vessels extending beyond the limbus for Placebo and Vitamin subjects.

Number of Hours	First Examination				Second Examination			
	Number		Per Cent		Number		Per Cent	
	Placebo Group	Vitamin Group	Placebo Group	Vitamin Group	Placebo Group	Vitamin Group	Placebo Group	Vitamin Group
Total	199	164	100.0	100.0	199	164	100.0	100.0
3					1		0.5	
4					2	2	1.0	1.2
5					1	1	0.5	0.6
6	1		0.5		3		1.5	
7		1		0.6	2	2	1.0	1.2
8	1	1	0.5	0.6	1	3	0.5	1.8
9	5	2	2.5	1.2	3	2	1.5	1.2
10	3	2	1.5	1.2	3	3	1.5	1.8
11	4	2	2.0	1.2	5	5	2.5	3.0
12	3	1	1.5	0.6	12	3	6.0	1.8
13	3	1	1.5	0.6	9	4	4.5	2.4
14	10	4	5.0	2.4	3	9	1.5	5.5
15	7	6	3.5	3.7	2	7	1.0	4.3
16	4	7	2.0	4.3	9	7	4.5	4.3
17	10	11	5.0	6.7	13	13	6.5	7.9
18	12	9	6.0	5.5	16	9	8.0	5.5
19	14	10	7.0	6.1	10	9	5.0	5.5
20	11	12	5.5	7.3	15	12	7.5	7.3
21	18	18	9.0	11.0	14	14	7.0	8.5
22	25	29	12.6	17.7	25	9	12.6	5.5
23	34	28	17.1	17.1	21	24	10.6	14.6
24	34	20	17.1	12.2	29	26	14.6	15.9
Mean No.	19.7	20.0			18.4	18.6		

In the following tables the Placebo and Vitamin groups are compared with respect to several different measures of the amount of corneal vascularization. The first four hundred examinations in the second examination period have been used for this analysis; and for some measures of vascularization only a part of the four hundred examinations have been tabulated. All

Table 18. Maximum number of arcades of vessels within cornea at any sector for Placebo and Vitamin groups.

Number of Arcades	First Examination				Second Examination			
	Number		Per Cent		Number		Per Cent	
	Placebo Group	Vitamin Group	Placebo Group	Vitamin Group	Placebo Group	Vitamin Group	Placebo Group	Vitamin Group
	MAXIMUM ARCADES IN EITHER EYE (CASE NUMBERS 1–100)[1]							
Total	45	50	100.0	100.0	45	50	100.0	100.0
2	4	10	8.9	20.0	6	12	13.3	24.0
3	25	26	55.6	52.0	20	26	44.4	52.0
4	15	11	33.3	22.0	14	7	31.1	14.0
5	1	2	2.2	4.0	3	2	6.7	4.0
6		1		2.0	2	3	4.4	6.0
Mean No.	3.3	3.2			3.4	3.2		
	MAXIMUM ARCADES COMMON TO BOTH EYES (CASE NUMBERS 101–400)[1]							
Total	154	114	100.0	100.0	154	114	100.0	100.0
1	10	2	6.5	1.8	9	7	5.8	6.1
2	55	39	35.7	34.2	77	55	50.0	48.2
3	66	60	42.9	52.6	54	37	35.1	32.5
4	22	12	14.3	10.5	14	13	9.1	11.4
5	1	1	0.6	0.9		2		1.8
Mean No.	2.7	2.7			2.5	2.5		

[1] Subjects receiving vitamins for less than nine months are excluded.

tables are based on a consecutive series of examinations. Subjects in the Vitamin group who had had therapy for less than nine calendar months before their second examination are excluded in comparisons of the two groups. Some of the first four hundred subjects examined did not have the first examination and these are omitted in tables showing results at both examinations.

If the extent of capillary invasion of the cornea is measured by totaling the number of hours occupied by capillary loops, the distribution shown in Table 17 is obtained. There is no significant difference between the means or the distributions for the Placebo and Vitamin groups. All subjects had some corneal vascularity, and in most cases it was extensive. The mean number of hours of arcades at the second examination was 18.4 and 18.6 for Placebo and Vitamin groups, respectively. In both groups there is a slight and approximately equal decrease in the mean between the first and second examination. This may have been due to a difference in grading in the two examinations or to unknown factors other than therapy, but the difference is not statistically significant.

Table 18 shows distributions of the maximum number of arcades within the cornea at any hour. Two ratings are shown, one for the maximum number of arcades in either eye (the worse eye) and the other the maximum number common to both eyes. The former gives a somewhat higher rating with an average maximum of slightly over 3 arcades at the second examination, compared with an average maximum of 2.5 arcades common to both eyes. There is no difference between the Placebo and Vitamin groups on either rating.

Vascularization in three divisions of the cornea, namely, between the hours 10 to 2 or upper sector, between hours 4 to 8 or lower sector, and between hours 2 to 4 and 8 to 10 or lateral sectors, is shown in Tables 19 and 20. In these tables, vascularization is measured for the right eye only. Both the number of arcades,

Number of Arcades	Between Hours 2–4 and 8–10				Between Hours 10–2				Between Hours 4–8			
	Number of Cases		Per Cent		Number of Cases		Per Cent		Number of Cases		Per Cent	
	Placebo	Vitamin	Placebo	Vitamin	Placebo	Vitamin	Placebo	Vitamin	Placebo	Vitamin	Placebo	Vitamin
Total	113	82	100.0	100.0	113	82	100.0	100.0	113	82	100.0	100.0
0	8	3	7.1	3.7					6		5.3	
1	37	29	32.7	35.4	4	2	3.5	2.4	26	18	23.0	22.0
2	56	32	49.6	39.0	40	30	35.4	36.6	60	49	53.1	59.8
3	12	17	10.6	20.7	43	35	38.1	42.7	20	15	17.7	18.3
4					24	7	21.2	8.5	1		0.9	
5		1		1.2	2	7	1.8	8.5				
6						1		1.2				
Mean No.	1.64	1.82			2.82	2.88			1.86	1.96		

Table 19. Maximum number of arcades in different sectors of right eye at second examination (case numbers 1-200).

Table 19, and the maximum extension[10] of arcades from limbus, Table 20, are greatest in the upper sector between the hours 10 to 2. In the lower sector, vascularization was only slightly greater than in the lateral sectors; the difference is consistent in both Placebo and Vitamin groups.

In each sector both the average number of arcades and the extension of arcades were somewhat greater in the Vitamin than in the Placebo subjects. The difference was least in the upper sector where the maximum vascularization occurred. In no sector is the difference between the mean number of arcades in the Placebo and Vitamin groups significant, but for the lateral sectors, hours 2 to 4 and 8 to 10, the percentage of Vitamin subjects with 3 or more arcades of vessels is significantly higher than the corre-

[10]Extension of arcades was measured in arbitrary units with 15 units to 1 mm. Measurements were recorded in whole numbers and were heavily concentrated on multiples of 5 units with a fair number of unit readings at mid-values between them as, for example, 7 or 8 units, but with very few other measurements, such as 6, 9, or 11. Therefore, in Table 20, measurements are grouped around mid-point values of 2.5 (2 or 3 units), 5 (4, 5, or 6 units), etc.

sponding percentage for Placebo subjects, the statistical probabil-

Table 20. Maximum extension of arcades observed in specified sector of right eye at second examination (case numbers 1-200).

Maximum Extension in Arbitrary Units, (1mm.=15 Units)	Between Hours 2-4 and 8-10		Between Hours 10-2		Between Hours 4-8	
	Placebo	Vitamin	Placebo	Vitamin	Placebo	Vitamin
	per cent					
Total	100.0	100.0	100.0	100.0	100.0	100.0
0	7.1	3.7			5.3	
2.5	0.9	1.2			2.7	
5	19.5	14.6			8.8	7.3
7.5	35.4	36.6	1.8	1.2	19.5	24.4
10	27.4	31.7	13.3	1.2	45.1	40.2
12.5	6.2	9.8	12.4	18.3	11.5	20.7
15	3.5	2.4	48.7	56.1	6.2	2.4
17.5			0.9	2.4	0.9	2.4
20			21.2	19.5		1.2
22.5			0.9			
25			0.9	1.2		1.2
	number					
Total	113	82	113	82	113	82
0	8	3			6	
2.5	1	1			3	
5	22	12			10	6
7.5	40	30	2	1	22	20
10	31	26	15	1	51	33
12.5	7	8	14	15	13	17
15	4	2	55	46	7	2
17.5			1	2	1	2
20			24	16		1
22.5			1			
25			1	1		1
Mean	7.70	8.26	15.13	15.55	9.00	10.42[1]
Stand. Deviation	3.28	2.93	3.45	2.86	3.48	3.35

[1] Mean extension is significantly greater ($P<.01$) for the Vitamin group.

Number of Hours of Streamer Arcades	Number of Persons		Per Cent of Total	
	Placebo Group	Vitamin Group	Placebo Group	Vitamin Group
Total	107	85	100.0	100.0
0	18	7	16.8	8.2
1–3	33	29	30.8	34.1
4–6	20	21	18.7	24.7
7–9	20	11	18.7	12.9
10–12	6	4	5.6	4.7
13–15	6	7	5.6	8.2
16–18	1	3	0.9	3.5
19–21	1	1	0.9	1.2
22–24	2	2	1.9	2.4
Mean No.	5.1	6.1		

Table 21. Total number of hours (both eyes) of streamer-type arcades of vessels in cornea at second examination for persons in Placebo and Vitamin groups (case numbers 201-400).

ity being about 3 chances in 100 for the difference to be due to chance. The difference between the average extension of arcades for the two groups is statistically significant only in the lower sector, between the hours 4 to 8.

The streamer type of arcades was stated (53) to be particularly indicative of ariboflavinosis. These are active capillaries which extend some distance along the cornea and then loop back. Often the arterial limb is much smaller than the venous limb, and the latter may be mistaken for a free-ending capillary. The results recorded in Table 21 show that the mean of the total number of hours of arcades of streamer type for the Vitamin group is slightly higher than that for the Placebo group.

The finding that corneal vascularity decreased with age (Table 22) is the reverse of what might be expected if corneal vascularity were indicative of vitamin deficiency, for a sign of a chronic lack would be expected to accumulate with age. This trend has been confirmed in an independent survey conducted among a

Number of Hours of Arcades	Number[1] of Persons by Age			Per Cent of Total by Age		
	19–29	30–39	40–49	19–29	30–39	40–49
Total	248	118	32	100.0	100.0	100.0
1–3			1			3.1
4–6	2	5	2	0.8	4.2	6.2
7–9	6	4	3	2.4	3.4	9.4
10–12	15	13	6	6.0	11.0	18.8
13–15	25	9	3	10.1	7.6	9.4
16–18	46	20	10	18.5	16.9	31.2
19–21	55	25	4	22.2	21.2	12.5
22–24	99	42	3	39.9	35.6	9.4
Mean No.	19.2	18.1	14.4			

[1] Includes subjects with no first examination and those on therapy who had received vitamins irregularly.

Table 22. Vascularity of cornea according to age. Total number of hours of arcades in both eyes at second examination for Placebo and Vitamin groups combined.

group of male employes of Los Angeles County (Table 23). These results appear to be in conflict with the data presented by

Table 23. Vascularity of cornea according to age among male employees of Los Angeles County. Total number of hours of arcades in both eyes.

Number of Hours of Arcades	Number of Persons by Age					Per Cent of Total by Age				
	19–29	30–39	40–49	50–59	60–69	19–29	30–39	40–49	50–59	60–69
Total	6	30	38	32	12	100.0	100.0	100.0	100.0	100.0
1–3			1	2				2.6	6.3	
4–6		5	5	2	2		16.7	13.2	6.3	16.7
7–9		5	7	6	5		16.7	18.4	18.8	41.7
10–12		3	5	5			10.0	13.2	15.6	
13–15		4	6	4	2		13.3	15.8	12.5	16.7
16–18	1	5	5	4	1	16.7	16.7	13.2	12.5	8.3
19–21	4	5	6	6	2	66.7	16.7	15.8	18.8	16.7
22–24	1	3	3	3		16.7	10.0	7.9	9.4	
Mean No.	20.0	13.6	13.1	13.4	11.3					

Scarborough (61), showing that circumcorneal vascularity was greater in patients over 50 years of age. It is not clear whether Scarborough and we used the same criterion of corneal vascularity. Scarborough used the term "circumcorneal"; we have taken as positive only those vessels which appeared to extend definitely across the limbus into the cornea.

The report of the first examination (2) discussed in some detail whether the presence of corneal vascularity may be taken as evidence of riboflavin deficiency, and cited a number of workers who questioned the reliability of this sign.[11] The results obtained with a more refined technique on the second examination show that corneal vascularity in subjects such as ours, nearly all of whom had this sign and few or no other signs of riboflavin deficiency, did not improve to any significant degree after a daily intake of 10 mg. of riboflavin five days a week for nine to twelve months. We must conclude that corneal vascularity, even as extensive as that seen in a large proportion of our subjects, may not be taken as evidence of existing riboflavin deficiency.

Kruse, *et al.* (52) and Sydenstricker, *et al.* (53) described ocular symptoms such as burning, irritation, and lachrimation as frequent concomitants of corneal vascularity in their cases of ariboflavinosis. On the other hand, of the thirty-one cases reported by Gregory (55) as showing "corneal vascularization compatible with ariboflavinosis," only five complained of these symptoms.

Tisdall, *et al.* (54) reported improvement in ocular symptoms and lessening of corneal vascularity following riboflavin therapy. Included in the evidence are photographs taken before and after therapy. The vascularity shown in these photographs was the same as that in our subjects. The photographs taken after riboflavin supplementation of 3.3 mg. daily for two months show un-

[11]Keys, *et al.* (62) erroneously ascribed to us: "The extreme view that all capillary infiltration of the cornea indicates active or chronic riboflavin deficiency. . . ."

questionably less engorgement of the limbal vessels than before therapy; but they are not convincing that there were fewer vessels in this region. Another possible reading of these photographs is not that there were fewer corneal vessels after therapy, but only less engorgement. Pirrie (63) made a similar criticism of the photographic evidence, and commented on the apparent paradox that, if the conclusions of Tisdall, *et al.* are accepted, the nutritional status of R.C.A.F. and civilian personnel in Canada must have been much worse than in Britain during wartime.

In a later study the same authors with Nicholls (64) found that the symptoms were improved in only five of twenty-three treated cases, and that there was no connection between corneal vascularization and the presence or absence of eye symptoms, and stated:

> "So far as this study shows, it seems that a uniform peripheral corneal vascularization is not a safe basis for a diagnosis of riboflavin deficiency existing at the time of the examination." and "Whether it is possible to reverse completely the pathological process and have empty blood vessels absorbed is, in the clinical experience of one of the authors (Nicholls) extremely doubtful."

Corneal vascularity did not develop in three independent studies of experimentally induced riboflavin deficiency in man. In these studies the deficient diets contained 0.47 mg. of B_2 daily (65); 0.35 mg. per 1,000 calories (66); and 1.0 mg. daily (67).

In a population in which 80 to 95 per cent had some degree of corneal vascularization, Sanstead (67) found no difference in corneal vascularization between the placebo controls and those who received 15 mg. of riboflavin daily for 60 to 110 days. Machella and McDonald (68) observed no beneficial effect of riboflavin therapy on the cheilosis, the ocular symptoms, or on the corneal vascularity in patients with vitamin B complex de-

ficiency. Goldsmith reported negative results of riboflavin therapy on corneal vascularization in patients with other signs of B complex deficiency (69). Similar, essentially negative, results were found by Pett (45) and by Ruffin (70).

Johnson and Eckhardt (71) and Johnson (72) reported disappearance of corneal vascularity with riboflavin therapy in cases of rosacea keratitis, and concluded that this disease was essentially a form of ariboflavinosis.

Wise (73), Fish (56), and Mann (57) disagree with Johnson and Eckhardt on every point. They concluded that rosacea keratitis is not a manifestation of ariboflavinosis, that the form of the corneal vascularity is quite different in the two conditions, and that specific signs of rosacea keratitis do not disappear with riboflavin and do so with other therapy. They support their conclusions with evidence adduced from controlled therapeutic trials in a large number of cases. Machella and McDonald (68) failed to obtain a favorable therapeutic response in cases of rosacea keratitis with riboflavin therapy, and Holt and Najjar (46) saw a positive response in only two of thirty-two cases.

It may be argued against the reported negative results of riboflavin therapy on corneal vascularization that the period of therapy was too short. But the positive results were reported to have occurred in a few days to a few weeks (52, 53). The studies which reported negative results were carried on for as long or longer periods and the doses of riboflavin used were as large. In our Study the period of riboflavin supplementation, nine to twelve months, was longer than in any yet reported. The initial corneal vascularity in many of our subjects was severe by the criteria of Kruse, *et al.* (52) and Sydenstricker, *et al.* (53). Few of them had any other sign of riboflavin deficiency. They would have been classified by the latter authors as the early or mild, chronic stage of riboflavin deficiency. If that were so, it is reasonable to expect a noticeable if small dif-

ference between our Placebo and Vitamin groups after nine to twelve months' therapy. None was found. It seems unlikely, therefore, that a longer period of therapy would have been any more effective.

In concluding this section, it is necessary to cite reports by critics of Kruse and Sydenstricker of cases in whom corneal capillaries were seen to empty as a result of riboflavin therapy (55, 56, 57, 74). There were few such cases, however, and the authors caution against making a diagnosis of ariboflavinosis on the basis of this and other signs without a therapeutic test. The same position is taken by Youmans and Patton (75).

Vitamin B Complex Deficiency: Signs on Lips and Face

A number of abnormal conditions of the lips and face have been proved to be associated with a deficiency of one or more members of the vitamin B complex. None of these signs appears to be specific for deficiency of any one vitamin.

The following complex of conditions is commonly associated with a deficiency of riboflavin, i.e., it was cleared up by riboflavin therapy: excessive vertical fissures of the lips, particularly of the lower lip, shiny, denuded, "chapped" lips with the line of closure very red (cheilosis), transverse fissures at the sides of the mouth, sebaceous plugs, seborrheic changes at the angles of the nose and eyes (fine, scaly, greasy desquamation on a mildly erythematous base), and a characteristic magenta coloring of the tongue (76, 77, 78, 79).

These signs evidently are the result of severe deficiency, as Williams, *et al.* (66) reported that the mouth, lips, tongue, and face remained normal after 288 days on a diet containing only 0.36 mg. per 1,000 calories, and no abnormal signs appeared on a superadded deficiency of thiamin, pyridoxin, niacin, and pantothenic acid. In the induced riboflavin deficiency of Boehrer, *et al.* (65), in which even less riboflavin was supplied, less than

0.5 mg. daily, only an apthous stomatitis and no other signs appeared. On the other hand, in the experiment of Egana, *et al.* (80), in which there was a total deficiency of the vitamin B complex, two of seven subjects developed cheilosis and scaling at the angles of the nose after three weeks, and these conditions disappeared in a few days when 36 gm. of dry yeast was eaten daily.

The angular stomatitis may be caused by mechanical trauma from artificial dentures (81). The glossitis may be indistinguishable from pellagra (82) the glossitis and cheilosis may occur in patients with normal B_2 and subnormal niacin excretion levels; and the cheilosis may respond to pyridoxin or niacin and not to riboflavin (82, 83, 84).

Grossman (85) reported a case of seborrheic dermatitis of the face and hands which was completely cleared by moderate doses of the whole vitamin B complex, after yeast alone or yeast plus nicotinic acid had brought only partial improvement.

Kuo and Huang (86) reported many cases of stomato-glossitis among refugees in China. The characteristic picture in their cases was numbness of the lips and tongue, painful cracks and fissures at the angles of the mouth, acute inflammation of the tongue with edema showing impressions of the teeth and hard palate, and hypertrophy of the papillae progressing to atrophy leaving an atrophic pale red, smooth tongue. The stomato-glossitis responded well to liver extract; nicotinic acid was often ineffective. The angular stomatitis did not respond to liver therapy, but it improved later as the appetite of the patients increased.

The above conditions of the lips and face were noted at the first and second examinations; abnormal conditions of the tongue are dealt with separately below. The findings are summarized in Table 24. The frequency of lesions of the face and lips was quite low, except for sebaceous plugs. The higher preva-

lence of sebaceous plugs noted at the second examination is probably because the slightest degree was recorded as positive at the second examination and not at the first. The sebaceous plugs did not have the characteristic "sulphur flake" appearance seen in pellagrins described by Smith, *et al.* (77). There were no statistically significant differences between the Placebo and Vitamin groups at either the first or second examinations. The only suggestive results are a lower prevalence of seborrhea or sebaceous plugs in the nasolabial folds and of fissures and abnormal coloring of the lips in the Vitamin group at the second examination. One of these three signs (one Placebo subject had both fissures and seborrhea of the nasolabial fold) was noted for

Table 24. Frequency of conditions or signs attributed to deficiency of vitamins of the B complex noted in Placebo and Vitamin groups at first and second examinations.

Condition	Number of Cases				Per Cent of Total Examined			
	First Examination		Second Examination		First Examination		Second Examination	
	Placebo	Vitamin	Placebo	Vitamin	Placebo	Vitamin	Placebo	Vitamin
Number of Persons Examined	255	258	259	262	100.0	100.0	100.0	100.0
Lips:								
Fissures	6	5	7	4	2.4	1.9	2.7	1.5
Ulcers	0	2	3	6	0	0.8	1.2	2.3
Seborrhea	2	3	0	3	0.8	1.2	0	1.2
Roughness, Dryness	2	3	1	1	0.8	1.2	0.4	0.4
Color Red, Purple	0	0	5	0	0	0	1.9	0
Nasolabial Folds:								
Seborrhae, Sebaceous Plugs	13	15	31	22	5.1	5.8	12.0	8.4
Ulcers	0	0	1	1	0	0	0.4	0.4
Comedones	*	*	4	4	*	*	1.5	1.5
Roughness, Dryness	0	0	11	12	0	0	4.3	4.6
Face:								
Seborrhea, Sebaceous Plugs	5	7	32	38	2.0	2.7	12.4	14.5
Total Persons With One or More of These Signs	23	28	72	68	9.0	10.9	27.8	26.0

*Comedones were not recorded on first examination.

16.2 and 9.9 per cent of the Placebo and Vitamin groups, respectively, and the difference is significant (P is .02 - .05).

Vitamin B Complex Deficiency: Changes in the Tongue

The glossitis in different vitamin B complex deficiency conditions, sprue, and pernicious anemia, has been described frequently. These are severe deficiency conditions which did not occur in our subjects. Our diagnostic problem was of possible mild, chronic deficiency. After we had completed the first examinations, the report of a study by Kruse appeared, which described in fine detail gross and microscopic changes in the tongue which were assigned to different stages of acute and chronic niacin deficiency (87). These stages, in brief, are as follows:

> "In the acute forms, vascular hyperemia and proliferation, hypertrophy, and then extinction occur successively in the papillae. The vascularity and hypertrophy of the fungiform papillae impart to the tongue the familiar stippled, then the strawberry aspect. . . . . Redness and swelling, marginal indentation, and then baldness manifest themselves in the tongue. In the chronic form, the stages of progression in the papillae are: vascular hyperemia and proliferation; infiltration; and atrophy. As the chronic process advances, the tongue itself shows fissures, crevices, and loss of substance, producing generally a thin tongue with marginal serrations." (87).

Sevringhaus and Kyhos (88), confining themselves to gross inspection of the tongue, followed the effects of 50 mg. niacinamide daily in twenty cases who had no evidence of acute pellagra but whose tongues did have characteristics which Kruse interpreted as evidence of chronic aniacinosis. In the course of nineteen weeks of this therapy, seventeen of the twenty showed improvement. The most striking and most frequent improvement was in the papillae, where the change was from virtual absence to a normal appearance. The fissures became shallower, though no tongue which was fissured lost all its marking. The authors cite (without description) cases with fissuring which

did not respond to niacin therapy; and believe, accordingly, that there may be other causes of fissuring of the tongue besides aniacinosis.

Our first examination discovered in 1,153 subjects only 24 (2.1 per cent) with one or more signs on the tongue which may be associated with a deficiency of niacin or other members of the vitamin B complex. The signs noted were abnormal redness, atrophy of papillae, absence of coating, edema, or hypertrophy. They were observed by gross inspection only, and only marked abnormalities were noted.

At the second examination the observations on the tongue

Table 25. Signs on the tongue attributed to niacin or vitamin B Complex deficiency.

Tongue Findings Attributed to Vitamin B Complex Deficiency	Number of Cases				Per Cent of Total Examined			
	First Examination		Second Examination		First Examination		Second Examination	
	Placebo	Vitamin	Placebo	Vitamin	Placebo	Vitamin	Placebo	Vitamin
Number of Persons Examined	244	261	244	261	100.0	100.0	100.0	100.0
Abnormal Redness[1]	0	1	101	84	0	0.4	41.4*	32.2
Atrophy of Papillae (Baldness)	0	0	4	4	0	0	1.6	1.5
Hypertrophied (Cobblestone)	[a]	[a]	32	14			13.1**	5.4
Abnormal Thickness	4	3	42	30	1.6	1.1	17.2	11.5
Number of Persons with One or More Signs	4	4	134	111	1.6	1.5	54.9**	42.5
Number of Persons with Two or More Signs	0	0	42	19	0	0	17.2**	7.3
Per Cent of Number Having Any Signs							68.7*	82.9
With One Sign								
With Two or More Signs							31.3*	17.1

[a] Observed with biomicroscope; not done on first examination.

[1] Includes cases designated red, strawberry, purple, magenta, scarlet red, and rust red in any area, including edges, margins, and tip.

* The probability that the observed difference in percentages for Placebo and Vitamin groups would occur by chance is between .01 and .05.

** The probability that the observed or a greater difference in percentages for Placebo and Vitamin groups would occur by chance is <.01.

took note of the lesser as well as the severe abnormalities. As a result, a higher frequency of all abnormalities was noted in both groups. In addition, the tongue was examined with the biomicroscope (low power). The outstanding abnormality observed was marked hypertrophy of the papillae. Under the microscope these papillae looked like cobblestones; most of the tongue was involved; and there were very few border-line cases. In most, but not all, cases the "cobblestone" effect was restricted to the fungiform papillae; when the filiform papillae were involved their cornification was defective or absent.

Findings on the tongue at the first and second examinations are presented in Table 25. At the first examination, one or more of the tongue signs was noted in only four persons in each group. At the second examination, the Placebo group had a significantly higher prevalence of abnormal redness and of hypertrophied papillae, and also a higher prevalence of abnormal thickness, but the difference was not statistically significant. The abnormal redness was confined in most cases to the tip and sides and included purple, magenta, strawberry, and abnormally bright red coloring. The prevalence of tongue signs noted at the second examination was very high; 55 per cent of the Placebo and 43 per cent of the Vitamin group had one or more of the signs.

This difference between the Placebo and Vitamin groups suggests a therapeutic effect of the vitamin supplement; but, as in the instance of follicular hyperkeratosis, the absence of comparable records on the first examination prohibits a definite conclusion. As far as they go, the results in Table 25 corroborate the findings of Kruse (87). But we wish to emphasize that we consider them only as a suggestion which needs to be tested by controlled therapeutic trial.

Vitamin C Deficiency: Plasma Ascorbic Acid

The values obtained for plasma ascorbic acid at the first and

Concentration Mg. Per Cent	Percentage Distribution		Cumulative Percentages		Number of Cases	
	Placebo Group	Vitamin Group	Placebo Group	Vitamin Group	Placebo Group	Vitamin Group
First Examination						
0.00–0.19 Mg.	10.8	12.5	10.8	12.5	29	33
0.20–0.39	22.4	19.7	33.2	32.2	60	52
0.40–0.59	18.3	20.8	51.5	53.0	49	55
0.60–0.79	19.8	14.8	71.3	67.8	53	39
0.80–0.99	12.3	14.0	83.6	81.8	33	37
1.00–1.19	8.9	9.8	92.5	91.6	24	26
1.20–1.39	3.4	6.8	95.9	98.4	9	18
1.40–1.59	2.2	0.8	98.1	99.2	6	2
1.60 or More	1.9	0.8			5	2
Total	100.0	100.0	100.0	100.0	268	264
Second Examination						
0.00–0.19 Mg.	2.6	0	2.6	0	7	0
0.20–0.39	13.4	0	16.0	0	36	0
0.40–0.59	21.3	0.4	37.3	0.4	57	1
0.60–0.79	22.8	1.1	60.1	1.5	61	3
0.80–0.99	16.0	1.1	76.1	2.6	43	3
1.00–1.19	11.6	23.9	87.7	26.5	31	63
1.20–1.39	8.2	37.5	95.9	64.0	22	99
1.40–1.59	3.0	25.4	98.9	89.4	8	67
1.60 or More	1.1	10.6			3	28
Total	100.0	100.0	100.0	100.0	268	264

Table 26. Plasma ascorbic acid concentration at first and second examinations of employees in Placebo and Vitamin groups.

second examinations are shown in Table 26. The technique[12] was the same at both examinations.

The values tended to be a little higher at the second examination in the Placebo group, although the general quality of the diets of both groups was essentially the same at the beginning and end of the Study year (3).

The plasma ascorbic acid values in the Vitamin group on the second examination were, of course, much higher than at the

[12]Determinations were made by the photelometric method on macro samples.

first examination, and much higher than in the Placebo group at either examination. This was to be expected, as the Vitamin group subjects received a supplement of 250 mg. of ascorbic acid daily five days a week.

The high plasma ascorbic acid values in the Vitamin group at the second examination testify only to their having ingested the supplement regularly. The four subjects with less than 0.80 mg. per cent of ascorbic acid were not on the swing shift and the dispensers could not give them their supplements directly. They may have taken their therapy irregularly after being transferred from the swing shift.

There are serious difficulties in assessing the significance of plasma ascorbic acid values in the appraisal of nutritional status. These were discussed in the report of the first examination (2). In human subjects on diets devoid of vitamin C, the plasma ascorbic acid values fall to zero within a month, yet no clinical signs appear for several months afterwards (29). Fox's observations on South African natives were similar. His subjects were living on the brink of scurvy; 12 of 950 developed scurvy. They all had little or no plasma ascorbic acid, yet no infallible pre-scorbutic signs were found (89).

Nevertheless, there is an impression among clinicians and pediatricians that plasma ascorbic acid values below 0.4 mg. per cent represent inadequate nutritional status with respect to vitamin C. This impression finds support in the observations of Kruse on the signs in the gums of mild, chronic pre-scorbutic states (90), and in the observations of Kyhos, *et al.* (91). The latter workers found good agreement between plasma ascorbic acid level, gum conditions and improvement in the gums at different levels of vitamin C supplementation. None of their subjects had scurvy; some improvement in the gums was obtained with a 25 mg. daily supplement; full improvement did not occur until a 75-100 mg. supplement was taken daily. When the supplement

was withdrawn, within four or five weeks, when the plasma ascorbic acid had fallen to 0.2 mg. per cent or less, the gums which had become normal on an adequate supplement of vitamin C again became puffy, abnormally red or cyanotic.

Unfortunately, our first examinations were completed before the work of Kruse and of Kyhos, *et al.* on pre-scorbutic signs in the gums had appeared. At the second examination, abnormal redness of the gums, even some bleeding on pressure, was found in both the Placebo and Vitamin groups. Recession of interdental papillae, punctate depressions, and atrophy of the gums were common in both groups. But the complication of very poor dental condition was so frequent that we felt unable to make any worth while comparisons between the two groups. Our Study, therefore, contributes no data on the question of the significance of plasma ascorbic acid levels.

Hematological Findings

Hemoglobin concentration and red cell volume were determined on nearly all the subjects at both examinations. Red cell counts were done on only about one-fifth of the subjects in the first examination, and for these the counts were repeated if they were available for the second examination.

In spite of the use of apparently identical techniques[13] on both examinations, at the second examination the hemoglobin values tended to be higher and the red cell volumes and red cell counts lower in both the Placebo and Vitamin groups. It is clear, nevertheless, from the figures in Table 27 that for those who had hemoglobin values less than 14.0 gms. at the first examination, no therapeutic effect on the hematological picture can be ascribed to the vitamin supplement.

[13]In the first examination, colorimetric readings for hemoglobin were made on a Sheard-Sanford photoelectric colorimeter, and in the second examination a spectrophotometer was used. Otherwise, the technique was the same. Both instruments were calibrated at the beginning of the examination period by oxygen combining capacity determinations.

Table 27. Average hematological values at second examination for persons in the Placebo and in the Vitamin groups, and comparison of groups on the basis of change in individual values between first and second examinations.

Blood Determination and Group	Number	Mean Value 2nd Exam.	Differences in Individual Values, 2nd–1st Exam.		Difference in Mean Change (P–V) and St. Error of Diff.
			Mean	Standard Error	
	TOTAL PERSONS				
Hemoglobin, Gms.					
Placebo	251	15.49	+1.07	.0505	+.09±.071
Vitamin	252	15.31	+0.98	.0514	
Volume of R.B.C., Per Cent					
Placebo	250	46.84	−0.83	.1402	+.49±.197*
Vitamin	252	46.51	−1.32	.1378	
*R.B.C. Millions p. Mm.*³					
Placebo	68	5.27	−0.44	.0663	−.16±.092
Vitamin	75	5.24	−0.28	.0638	
	PERSONS WITH HEMOGLOBIN VALUES LESS THAN 14.0 GMS. AT 1ST EXAM.				
Hemoglobin, Gms.					
Placebo	63	14.67	+1.32	.1069	+.07±.149
Vitamin	79	14.67	+1.25	.1024	
Volume of R.B.C., Per Cent					
Placebo	62	44.82	−0.13	.2450	+.52±.353
Vitamin	79	44.92	−0.65	.2470	
*R.B.C. Millions p. Mm.*³					
Placebo	30	5.06	−0.28	.0811	+.01±.125
Vitamin	45	5.14	−0.29	.0865	
	PERSONS WITH HEMOGLOBIN VALUES 14.0 GMS. OR MORE AT 1ST EXAM.				
Hemoglobin, Gms.					
Placebo	188	15.76	+0.99	.0559	+.14±.080
Vitamin	173	15.61	+0.85	.0561	
Volume of R.B.C., Per Cent					
Placebo	188	47.50	−1.06	.1649	+.57±.231*
Vitamin	173	47.23	−1.63	.1611	
*R.B.C. Millions p. Mm.*³					
Placebo	38	5.44	−0.57	.0957	−.31±.137*
Vitamin	30	5.40	−0.26	.0943	

* Probability of difference occurring by chance is .01-.05.

At the first examination, on the basis of the normal values given by Wintrobe (92), in the group as a whole there was a tendency toward low hemoglobin values, high red cell volume, and high red cell counts. The difference between the second and first examinations tended, in all three instances, to eliminate these aberrations from Wintrobe's normal values, i.e., the hemoglobin values were about 1.0 gm. higher, the red cell volumes 0.8-1.3 per cent lower, and the red cell counts 0.28-0.44 millions per cu. mm. lower. We are inclined, therefore, to ascribe the differences in hematological values between the first and second examinations to differences in technique. This possibility was recognized in the report of the first examination (2). We have no clue as to what the differences in technique may have been.

Reports on Symptoms

Medical histories were taken at both the first and second examinations. Most of the information obtained pertained to symptoms experienced within the three months preceding the interview. The reports at the two examinations are compared in Table 28.

In order to obtain some information on the psychotherapeutic effect of participation in an experiment, near the end of the Study year medical histories of a second control group were taken. The findings in this group are given in Tables 28 to 31 inclusive under "Control Group." The Control group did not participate in the Study; its members received neither the vitamin supplement nor the placebo; they were not examined at either time; and until their medical histories were taken they did not know they were being included in the Study. The composition of the Control group is described in the preceding report (3). It was selected to compare as closely as possible, with respect to age, duration and type of employment with employes in the Vitamin and Placebo groups who were direct production

Table 28. Reported history of the occurrence of various conditions and symptoms in the three months preceding the interview for the Vitamin group, the Placebo group, and a nonparticipating Control group.

Condition Reported	Per Cent of Total Persons Reporting				
	First History		Second History		
	Placebo	Vitamin	Placebo	Vitamin	Control
Eye Symptoms:					
Itch, Burn, Feel Gritty	35.3	42.2	44.0	51.3	33.0
Tire Easily	24.4	30.7	35.5	40.2	27.0
Sensitive to Light, Tear Easily	48.1	49.8	59.8	57.5	40.5
Stick Together	*	*	7.7	9.6	2.7
Gastro-Intestinal Symptoms:					
Indigestion	27.9	24.5	17.4	19.2	5.9
Gastric Pain	*	*	14.7	17.2	5.4
Heartburn	*	*	11.2	9.6	6.5
Constipation	23.6	25.3	16.2	14.6	10.8
Diarrhea	5.0	6.9	7.3	3.4	1.6
Nausea, Vomiting	*	*	12.4	13.0	2.2
No Gastro-Intestinal Symptoms			57.5	57.9	71.9
Easily Irritated	9.3	16.5	10.4	10.3	4.3
Fatigue:					
Tired All the Time	*	*	8.5	10.0	3.8
Tired After Work	*	*	35.1	38.3	47.0
Feels Like Going Out	*	*	57.9	58.2	64.3
Cramps in Calf Muscles	11.6	12.3	16.6	12.3	7.0
Burning Sensation in Hands or Feet	2.7	2.3	5.4	2.3	0
Pins or Needles in Fingers or Toes	4.7	2.7	8.1	10.7	1.6
Cramps, Burning Sensation, Pins or Needles	17.8	16.1	25.9	19.9	8.7
Headaches, Any Attacks	*	*	35.5	29.5	25.4
Nails Break Easily	*	*	12.4	18.8	13.5
Appetite:					
Good	56.2	58.6	63.6	70.9	68.6
Fair	37.2	36.4	33.3	24.9	26.5
Poor	6.6	5.0	3.1	4.2	4.9
Better[1]	*	*	49.4	60.2	20.5
Same	*	*	39.4	27.5	68.6
Worse	*	*	11.2	12.3	10.8
Number of Persons Reporting	258	261	259	261	185

* Conditions were not reported on first medical history.

[1] The difference between percentages of Vitamin and Placebo subjects reporting a "better" appetite is significant but is largely eliminated if the influence of different interviewers is controlled (*see* footnote 14). For both experimental groups, the percentages are very significantly higher than for the Control group.

workers (i.e., supervisorial and clerical staff were excluded) and who had remained on the swing shift throughout the Study year.

The differences between the Vitamin and Placebo groups for each symptom in Table 28 are small and not consistently in favor of either group. It is clear that there was no therapeutic effect of the vitamin supplement on symptoms when the comparison is based on reports made independently for the two periods (i.e., when the subjects were not asked to compare their symptoms at the second examination with those at the first).

In the Control group the frequency of symptoms felt was in all instances less than in either of the two experimental groups at their second examinations.

The medical histories of the Vitamin and Placebo groups were taken by five interviewers (the majority by two interviewers), and all of the histories for the Control group by one interviewer who took very few histories for subjects in the Study. Some differences between interviewers in rates for a number of symptoms were noted,[14] and, in order to obtain a more reliable comparison between the Control group and the Study groups, Table 29 is presented. The frequency of symptoms reported by those in the Control group is compared with rates for all Vitamin and Placebo subjects whose histories were taken by the same interviewer, and also is compared with the total Placebo group. These comparisons between the Control group and the two experimental groups, which did not differ, indicate the psychotherapeutic effect on the reporting of symptoms.

When histories taken by the same interviewer are used, the differences in the frequency of symptoms felt in the months preceding the interview between the Control group and the Study

[14]In order to control differences for the various interviewers, comparisons between the Placebo and Vitamin groups were made of rates based on histories taken by the same interviewer. Although the reported frequency of some symptoms differed for the different interviewers, there was no significant difference between the Placebo and Vitamin groups in findings from histories taken by the same interviewer. The differences between interviewers may have been due, in part, to a seasonal influence.

subjects are small in most instances. There is still a tendency for fewer persons in the Control group than in the Study to report symptomatic conditions, especially sensitivity of the eyes to light, indigestion, and fatigue. Only the difference or sensitivity to light is significant.

The difference between the experimental and Control groups is larger when they are compared with respect to subjective im-

Table 29. Frequency of conditions or symptoms reported by the nonparticipating Control group compared with frequency for persons in the Study interviewed by same investigator.

Condition or Symptom	Per Cent of Total Reporting Specified Condition		
	Control Group	Same Interviewer as Control Group Placebo+Vitamin	Total Placebo Group Five Interviewers
Eyes:			
Itch, Burn or Feel Gritty	33.0	31.5	44.0*
Tire Easily	27.0	24.1	35.5
Sensitive to Light, Tear Easily	40.5	61.1*	59.8**
Indigestion	5.9	11.1	17.4
Constipation	10.8	11.1	16.2
Fatigue:			
Tired All the Time	3.8	7.4	8.5*
Tired After Work	47.0	51.9	35.1*
Cramps in Calf Muscles	7.0	9.3	16.6
Headaches	25.4	33.3	35.5**
Appetite:			
Good	68.6	74.1	63.7
Fair	26.5	22.2	33.2
Poor	4.9	3.7	3.1
Better	20.5	53.7**	49.4**
Same	68.6	42.6	39.4
Worse	10.8	3.7	11.2
Number of Persons Reporting	185	54	259

* Rate is significantly higher (P.01-.05) than that for Control group.
** Rate is very significantly higher (P<.01) than that for Control group.

Examination and Study Group	Period of Interview	Number of Persons	Per Cent Reporting Specified Number of Colds				
			Total	None	One	Two	Three or More
First Examination							
Placebo	Nov. 14–Feb. 13	256	100.0	16.4	42.6	20.7	20.3
Vitamin	Nov. 14–Feb. 13	260	100.0	22.3	39.6	15.0	23.1
Second Examination							
Placebo	Dec. 15–Feb. 28	223	100.0	27.4	49.3	16.6	6.7
Vitamin	Dec. 15–Feb. 28	200	100.0	31.5	51.0	10.0	7.5
Second Examination							
Nonparticipating Control	March	194	100.0	36.6	45.9	9.8	7.7
Placebo	Feb. 1–April 2	122	100.0	38.5	44.3	12.3	4.9
Vitamin	Feb. 1–April 2	162	100.0	39.5	45.1	9.3	6.2

Table 30. Number of respiratory attacks reported for three months preceding interview by Placebo and Vitamin groups at first and second examinations and by nonparticipating Control group.

pressions of change in appetite compared with the year before. Approximately one-half or more of those in the experimental groups and only one-fifth of the Control group reported a better appetite than a year before; in each of the three groups about 11 to 12 per cent reported a worse appetite (Table 28). When histories taken by the same interviewer are compared (Table 29) the percentages with a better appetite are not changed, but the percentage in the experimental groups with a worse appetite is about 4 per cent compared with 11 per cent in the Control group. Thus, a significantly larger percentage of the Control subjects reported no change in appetite. A similar difference is obtained in the comparison of the subjects' impression of the relative frequency of colds in the two winter seasons (Table 31).

These findings from medical histories give evidence that participation in the experiment had some positive psychotherapeutic effects when subjects were asked to compare their present symp-

Group	Period of Interview	Number of Persons	Per Cent Reporting Specified Change			
			Total	Fewer Colds	No Change	More Colds
Placebo	Dec. 15–April 2	254	100.0	65.7	27.2	7.1
Vitamin	Dec. 15–April 2	257	100.0	68.9	24.5	6.6
Nonparticipating Control	March	194	100.0	26.3	57.7	16.0
Placebo	Feb. 1–April 2	119	100.0	72.3	22.7	5.0
Vitamin	Feb. 1–April 2	159	100.0	67.3	26.4	6.3

Table 31. Comparative frequency of colds in winter of 1942-1943 and in previous winter as estimated by persons in Placebo and Vitamin groups and by persons in a nonparticipating Control group.

toms with those a year before. When there was no estimate of change involved in the report on symptoms, there was a slight negative psychotherapeutic effect.

Respiratory Infections

Resistance to infection is impaired in states of severe deficiency of many vitamins (93, 94) and of protein (95). It is not as well established whether resistance is impaired, or convalescence prolonged, in the so-called suboptimal or latent deficiency states. The question commonly has taken the form whether or not vitamin supplementation of a common secular or institutional diet can reduce the incidence or duration of respiratory infections, especially of colds.

Gardner and Gardner (96) and Tress (97) reported positive effects in children of a supplement of 8,500 to 10,000 I.U. vitamin A daily for three months. Beard (98) reported a reduction in the number of colds in adults by a supplement of vitamins A and B; Cameron (99) found a slight decrease in the duration but not in the frequency of colds after a vitamin A supplement was given; Spiesman (100) obtained a reduction in both the frequency and

severity of colds in chronic sufferers with massive doses of vitamins A and D; in a five-year experiment Holmes, *et al.* (101) ascribed a decrease in absenteeism among industrial workers because of colds and other respiratory infections to a cod liver oil supplement.

In a controlled experiment (without placebo) on the effect of (with other factors), 2 mg. of B_2, 20 mg. niacinamide, 1,000 I.U. of a polyvitamin supplement (4,000 I.U. of A, 350 I.U. of thiamin C, and 600 I.U. of D) five times a week for thirty-seven weeks, on the health of school children, Kohn, *et al.* (29) found that there was significantly less infection in the Vitamin group. Crampton (102) reported "cure" of colds in twenty-four to forty-eight hours by 150,000 I.U. vitamin A and 1,500 I.U. vitamin D; Manwaring (103) reported almost as rapid a curative effect on colds of a single one gram dose of vitamin C. Kay (104) reported prevention of acute respiratory infections in the aged by multivitamin capsules containing 9,000 I.U. vitamin A, 900 I.U. vitamin D, and less than the Recommended Daily Allowances of B_1, B_2, and C.

Glazebrook and Thompson (105), by providing vitamin C to "saturation" as judged by urinary excretion to young men on a diet low in vitamin C, obtained a reduction in the incidence of tonsillitis (but not of colds) and reduction of stay in the sick room because of "infective conditions." Stone, *et al.* (106) observed a decrease in respiratory infections and improvement in general well-being in college students living on a poor diet when a moderate supplement of vitamins A, B_1, B_2, and D was given.

Negative results were obtained in carefully controlled studies (without placebos) on children, where the data were obtained by daily direct observation, by Wright, *et al.* (107), Barenberg and Lewis (108), Hess, *et al.* (109), Kuttner (110), and Bransby, *et al.* (111), and in adults by Sherman (112).

In all the foregoing studies the control was either the record

of a group in the previous year or years which was not always composed of the same subjects, or of a group judged to be comparable to whom no supplement was given. None employed a placebo control group. Placebo controlled studies were carried out by Gittleman and Wiener (113), Sibley and Spies (114), Cowan, *et al.* (115), Sutherland (116), and by Yudkin (117).

Sibley and Spies administered 200,000 I.U. vitamin A and 4,000 I.U. vitamin D weekly for 56 weeks to one group of 67 adults, vitamin D alone to 71, and a placebo of maize oil to 73. The incidence of colds was the same in all three groups; but their duration was least in the vitamin A and D group; and the difference between this group and the placebo group, 9.6 days as against 12.5 days per subject, was statistically significant. There was no effect of the vitamin D alone.

Cowan, *et al.* (115) carried out two studies in which placebo controls were used. In one the effect of 200 mg. daily of vitamin C was tested. The vitamin group averaged 1.9 colds and the placebo group 2.2 colds; the difference was of moderate statistical significance (P equals .03—.04). A year later (1940-1941) the effect of multivitamin capsules was tested; the capsules furnished a daily supplement of vitamin A 20,000 I.U., B_1 1.2 mg., B_2 0.2 mg., C 50 mg., and D 2,000 I.U. No difference was observed between the vitamin and placebo groups in the incidence or duration of colds. In both studies the vitamin group had a higher incidence of complications with their colds.

Cowan, *et al.* (115) and Diehl (118) reported a psychotherapeutic effect of participation in the experiment; their subjects knew that the object of the experiment was to test a prophylactic agent against colds. Both the vitamin and placebo groups had fewer colds than the general student body. A similar psychotherapeutic effect had been observed with saline injections as a control in a study of the effect of vaccines.

No prophylactic effect against colds was found in the placebo

controlled experiments on children of Gittleman and Wiener and of Sutherland, and they were inconclusive in Yudkin's study.

A fair summary of the foregoing appears to be that the results were negative in most of the adequately controlled studies of population groups where the diet was not seriously restricted (as in Britain during the war). Where a positive therapeutic (as distinguished from a psychotherapeutic) effect was observed, the absolute effect, i.e., reduction in number or duration of colds, was of little practical significance.

Our Study provides some data on this question. At the first examination only 16.4 and 22.3 per cent of the Placebo and Vitamin groups, respectively, reported having no respiratory infections during the previous three fall or winter months (Table 30). At the second examination, colds were generally less frequent than in the same season of the previous year; and there was no significant difference in frequency between the Placebo and Vitamin groups. Also, members of the Control group reported about the same numbers of colds as those in the two other groups.

There was, therefore, neither a therapeutic effect of the vitamin supplement, nor a psychotherapeutic effect of the experiment, on the frequency of respiratory infections. We had no way of checking the accuracy of our subjects' reports. The order of reliability is probably about the same as in most other studies on this subject.

In appraising any psychotherapeutic effect, one must distinguish between the actual manifestation and the subject's impression of what the effect has been. The impression in our subjects' minds of the relative frequency of colds during the fall and winter seasons at the end of the Study and the year before illustrates this point. In the second examination one question in the medical history was substantially: "Did you have more colds, the same number, or less, than in the same

months last year?" The replies to this question are summarized in Table 31. There was no difference between the Placebo and Vitamin groups. Many more in the two experimental groups reported that they had had fewer colds than the year before than in the Control group. The Control group was interviewed in the last month of the second examination period, and to minimize any seasonal effect, this group is compared in Table 31 with that part of each experimental group for which histories were taken in the last two months. The difference between the Control and experimental groups is not affected by season.[18]

It seems a reasonable conclusion that the difference in impression regarding the change in number of colds between the Control and the experimental groups was a psychotherapeutic effect of the experiment, and that this effect resided not so much in actual manifestation as in impression. It is interesting in this connection that in the second six months of the Study year the Control groups were absent on account of illness 2.99 days per 100 man days, whereas the comparable Placebo and Vitamin groups were absent in the same period for the same stated reason 1.89 and 1.92 days, respectively (3).

Our result that the vitamin supplement had no prophylactic effect against colds of any practical importance is in accord with all the placebo controlled studies of this subject. The psychotherapeutic effect was also negative, as judged by the reports of the Vitamin and Placebo groups on the one hand and of the nonparticipating Control group on the other, on the number of colds during the winter months at the end of the Study year. The psychotherapeutic effect was positive, as judged by the impression in the minds of the two experimental groups on the one hand and of the Control group on the other, regarding the

[18]There was little difference between the February and March interviews with respect to the percentages of persons reporting fewer colds in either experimental group. Not many experimental subjects were interviewed in March.

frequency of colds at the time of the second examination compared with that a year before.

Reports of Specific Benefits Ascribed to the Placebo or the Vitamin Supplement

At the end of the medical history of the second examination, every subject was asked if he felt that he had received any benefit from the "pills" he had been taking. If he stated that he had been benefited, he was asked "In what respects?" Otherwise no leading questions were asked. The answers received are summarized in Table 32. There were differences among the interviewers which affected the comparison of the Placebo and Vitamin groups to some extent and, therefore, replies obtained by two of the interviewers are shown separately, and for the total Placebo group a weighted per cent is given which adjusts this group to the Vitamin group according to the percentage of that group interviewed by each interviewer..[16]

The outstanding result is that over 70 per cent of the Placebo group reported being benefited in one or more respects, and they ascribed this benefit to the pills which they believed contained vitamins and minerals.[17] Thirty-one per cent of the Placebo group ascribed benefits of "feeling better, more energy, or less

[16]If the same percentage of the Placebo and Vitamin groups had been interviewed by each of the five interviewers, the groups as a whole would have been equally affected by any influence the interviewers may have had on replies concerning benefits or on recording a number of different benefits. To adjust for differences between the groups in the proportions interviewed by a specific investigator, a weighted value for the Placebo group was computed for each type of benefit, as follows: for persons in the Placebo group interviewed by a specific interviewer, the percentage reporting a particular benefit was computed; the percentage of the total Vitamin group interviewed by each investigator was computed; then the percentages with a particular benefit for the different interviewers were weighted by (multiplied by) the percentages in the Vitamin group interviewed by the same investigator, the products were summed and an average percentage computed for the Placebo group.

[17]It will be noted on comparing Tables 31 and 32 that although two-thirds of the Placebo and Vitamin groups reported fewer colds than the year before, only one-half of those who so reported ascribed this to either the placebo or vitamin pills. There is a similar difference between the number reporting "better appetite" when asked about change in appetite and the number mentioning improved appetite when asked to tell any benefits from the "pills."

Table 32. Per cent of subjects in Placebo and Vitamin groups reporting specified benefits.

Benefit Reported and Study Group	Per Cent Reporting as Specified				Weighted[1] Per Cent for Placebo Group	Difference, Weighted Per Cent for Placebo-Vitamin
	Interviewed by			Total Group		
	R	S	Others			
Number Reporting:						
Placebo	144	65	46	255		
Vitamin	95	109	53	257		
No Benefits						
Placebo Group	20.14*	36.92	28.26	25.88	29.16	+6.20
Vitamin Group	9.47	35.78	20.75	22.96		
Colds, Fewer or Less Severe						
Placebo Group	27.08	35.38	34.78	30.59	30.94	−2.13
Vitamin Group	35.79	33.94	26.42	33.07		
Appetite Improved						
Placebo Group	20.83	12.31	17.39	18.04	15.46	−4.77
Vitamin Group	21.05	20.18	18.87	20.23		
Other Benefits						
Placebo Group	65.28	52.31	50.00	59.22	56.78	−3.14
Vitamin Group	73.68	50.46	54.72	59.92		
Feel Better, More Energy, or Less Fatigue						
Placebo Group	35.42	24.62	28.26	31.37	30.50	−4.52
Vitamin Group	50.53*	22.94	32.08	35.02		
Less Nervous						
Placebo Group	3.47	0	0	1.96	1.28	−6.11
Vitamin Group	5.26	10.09**	5.66	7.39**		
Headaches						
Placebo Group	0.69	1.54	4.35	1.57	1.10	−2.79
Vitamin Group	4.21	1.83	7.55	3.89		
Eyes Better						
Placebo Group	20.83	15.38	19.57	19.22	19.52	+4.34
Vitamin Group	17.89	12.84	15.09	15.18		
Sleep Better						
Placebo Group	11.11	1.54	2.17	7.06	4.86	−0.20
Vitamin Group	6.32	5.50	1.89	5.06		
Weight Gain						
Placebo Group	6.94	10.77	8.70	8.24	9.23	+1.06
Vitamin Group	8.42	7.34	9.43	8.17		
Constipation Improved						
Placebo Group	4.86	0	0	2.75	1.80	−2.09
Vitamin Group	2.11	4.59	5.66	3.89		
Digestion Improved						
Placebo Group	4.17	0	2.17	2.75	2.54	−0.57
Vitamin Group	3.16	3.67	1.89	3.11		
Miscellaneous						
Placebo Group	2.08	4.62	6.52	3.53	4.35	+1.24
Vitamin Group	2.11	4.59	1.89	3.11		

[1] Average of the percentages for subjects interviewed by each investigator weighted according to the percentages of the total vitamin subjects interviewed by the same investigator.

* Probability of difference in rates being due to chance is .01-.05.

** Probability of difference in rates being due to chance is.<.01.

fatigue" to the pills, and 20 per cent felt their eyes were better for the same reason.

There was, of course, no way of telling whether the specific benefits ascribed to the placebo pills had any organic basis. The record of symptoms on the second examination (reported without reference to those a year before, Table 28) indicated that no improvement in symptoms had occurred. Nor did the second physical and instrumental examinations discover any evidence of organic improvement. The psychotherapeutic benefits reported, therefore, may have been merely an erroneous impression.[18] Whatever its basis, the impression had persisted to the end of the Study year, and as far as the feeling of well-being is concerned was evidently as real as if an organic basis had been demonstrated.

A slightly higher percentage of the Vitamin than of the Placebo group ascribed to the "pills" they had been receiving benefits with respect to colds, appetite, improvement in general well-being, nervousness, headache, constipation, and "digestion." The only difference which was statistically significant was with respect to feeling less nervous. The number of subjects in this category was small, 7.4 and 1.3 per cent of the Vitamin and Placebo groups, respectively.

More Placebo than Vitamin subjects reported benefits with respect to eyes, weight gain, and miscellaneous conditions which they ascribed to the pills. None of these differences were statistically significant.

Twenty-nine and 23 per cent of the Placebo and Vitamin groups, respectively, reported feeling no benefits. The difference is not statistically significant (P equals .12—.13).

[18] In any group, a certain number will feel better or have symptomatic improvement in one year as against the previous year. Since the men who received placebos thought they were getting vitamins and expected to be benefited, they would ascribe any improvement to the "pills." On the other hand, the number of men who thought they felt better or had experienced loss of symptoms seems large, especially in view of the fact that their reported prevalence of symptoms was as high or higher than that in the Control group.

The trend was toward more benefits reported by the Vitamin group, whether these are considered as a whole or in separate categories, but the superiority of the Vitamin group is not impressive.

Summary

A supplement containing six vitamins and calcium was given daily to a group of aircraft workers five days a week for nine to twelve months, and a placebo was given to a second group. There was a second control group of employes who did not participate actively in the Study. About 70 per cent of the subjects were under 30 years of age at the time the Study began.

The members of the Placebo and Vitamin groups were examined by clinical, instrumental, and laboratory methods at the beginning and again at the end of the Study. Medical histories were taken at both examinations. The methods employed in the examination and history were selected primarily for the appraisal of nutritional status.

Initially the Placebo and Vitamin groups were alike in age, duration of employment, diet, physical condition, and symptoms. The quality of the diets remained essentially unchanged. The Control group was comparable with respect to age, duration of employment, and type of work.

No cases of severe nutritional deficiency disease were found at either examination. The Study group as a whole would have been considered healthy by conventional general standards, having been selected for employment by rigorous pre-employment medical and psychological aptitude examinations. On the other hand, a majority of the subjects had evidence of chronic, mild nutritional deficiency by special criteria which have been proposed. One of the purposes of this Study was to evaluate these criteria in terms of their modification with prolonged therapy.

The data obtained are classified into three categories:

1. Data obtained both at the beginning and at the end of the Study which afforded comparisons of the status of the Placebo and Vitamin subjects separately at the beginning and at the end of the Study, as well as with each other.

2. Data obtained only at the second examination which afforded comparisons only between the Placebo and Vitamin groups at the end of the Study, i.e., at the time of the second examination.

3. Data on history of symptoms and minor illnesses and on the psychotherapeutic effects of participation in the Study.

Category 1. Comparisons of data obtained at both the first and second examinations show no significant, specific, therapeutic effects of the vitamin-mineral supplement with the exception of that for conjunctival opacity or thickening.

(a) Vitamin A deficiency: conjunctival opacity and elevations (observed with the biomicroscope). There is evidence suggesting that the loss of conjunctival transparency which was observed in all subjects was improved slightly by the vitamin-mineral supplement (vitamin A). An average rating for conjunctival translucency for Vitamin subjects showed a small but significantly greater improvement at the end of the Study than did the rating for Placebo subjects; and a larger percentage of the Vitamin than of the Placebo group had some improvement in fairly extensive portions of the conjunctivae.

(b) Thiamin deficiency: abnormalities in reflexes, calf muscle tenderness, plantar dysesthesia, and loss of vibratory sensibility to a C-256 tuning fork. No therapeutic effects were found.

(c) Riboflavin (or vitamin B complex) deficiency: cheilosis, angular stomatitis, sebaceous plugs, seborrheic dermatitis, and corneal vascularization (observed with the biomicroscope). For none of these signs was there statistically significant evidence of a therapeutic result, although seborrhea of the nasolabial folds and fissures and abnormal coloring of the lips were less frequent among the Vitamin than among the Placebo subjects.

(d) The plasma ascorbic acid levels were consistently much

higher in the Vitamin group at the second examination than at the first, and also than in the Placebo group at either examination. This effect was a result of the daily ingestion of 250 mg. of ascorbic acid. Our data do not contribute any information as to its clinical significance.

(c) There were no demonstrable hematological effects of the vitamin-mineral supplement. There were consistent differences in the hematological findings between the first and second examinations in both the Placebo and Vitamin groups, in the same direction and to the same degree in both groups. These differences cannot be accounted for; they are believed to be the result of unidentified differences in technique.

The data on the second examination give hematological values for the Study group as a whole more within the "normal" ranges than did those of the first examination.

Category 2. Data obtained only on the second examination pertained to the following:

(a) Vitamin A deficiency: dryness of hair and follicular hyperkeratosis. There was a significantly greater prevalence of dryness of hair, and a higher prevalence, more extensive, and more severe degrees of follicular hyperkeratosis in the Placebo than in the Vitamin group.

(b) Thiamin deficiency: thresholds of vibratory sensibility at different frequencies, and paresthesias evoked by vibratory stimulation. No differences were found between the Placebo and Vitamin groups.

(c) Vitamin B complex deficiency: tongue abnormalities. There was a higher prevalence of mild degrees of abnormal thickness, abnormal color, and hypertrophied papillae (observed with the biomicroscope) in the Placebo than in the Vitamin group. The differences were statistically significant for abnormal color and hypertrophied papillae.

As there were no comparable observations on the first examina-

tion, the apparent, positive therapeutic effects of the vitamin-mineral supplement on mild follicular hyperkeratosis and on glossitis may be considered only as suggestions which need to be tested by controlled therapeutic trial.

Detailed observation of these two conditions and conjunctival lesions were the only ones, of all the methods used in this Study, which appear to hold promise of reliable diagnosis of mild nutritional deficiency in a population such as the subjects of this Study, when judged by response to therapy for five days a week over a period of nine to twelve months.

Category 3. The data obtained from the medical histories on the first and second examinations revealed no improvement in symptoms and no reduction in the incidence of colds which could be ascribed to a therapeutic effect of the vitamin-mineral supplement.

Although the incidence of colds reported at the second examination for the previous three months was essentially the same in all three groups, many more in the Placebo and Vitamin groups than in the nonparticipating Control group reported that they had had fewer colds than the year before. Similarly, although about the same proportions of all three groups reported a "good" appetite, higher proportions of the experimental groups thought their appetite was better than the year before. It was concluded that this difference in subjective impression between the two experimental groups on the one hand and the Control group on the other, was a psychotherapeutic effect of participation in the experiment.

About 70 per cent of the Placebo group reported improvement in one or more symptoms, which they ascribed to the "pills" they had been taking. The medical histories taken at the second examination, in which the prevailing symptoms were reported without reference to those a year before, indicated neither so consistent nor so large a measure of improvement.

A larger number of the Placebo than of the Vitamin group reported benefits with respect to eye symptoms, weight gain, and miscellaneous conditions. A larger number of the Vitamin group reported benefits in eight categories: colds, appetite, feeling of well-being, less nervous, headaches, constipation, and improved digestion. Twenty-nine and 23 per cent of the Placebo and Vitamin groups, respectively, reported experiencing no benefits. The only statistically significant difference is that between percentages of subjects reporting less nervousness, 7.4 and 1.3 per cent, respectively, for the Vitamin and Placebo groups.

The pertinent literature is reviewed. The findings reported here (the positive and negative results) are in accord with the consensus of other studies.

References

1. Wiehl, Dorothy G.: Diets of a Group of Aircraft Workers in Southern California. The Milbank Memorial Fund *Quarterly*, October, 1942, xx, No. 4, pp. 329-366.

2. Borsook, Henry; Alpert, Elmer; and Keighley, Geoffrey: Nutritional Status of Aircraft Workers in Southern California. II. Clinical and Laboratory Findings. The Milbank Memorial Fund *Quarterly*, April, 1943, xxi, No. 2, pp. 115-157.

3. Borsook, Henry: Nutritional Status of Aircraft Workers in Southern California. III. Effects of Vitamin Supplementation on Absenteeism, Turnover, and Personnel Ratings. The Milbank Memorial Fund *Quarterly*, April, 1945, xxiii, No. 2, pp. 1-48.

4. Frazier, Chester N. and Hu, Chu'Uan-K'Uei: Cutaneous Lesions Associated with a Deficiency in Vitamin A in Man. *Archives of Internal Medicine*, September, 1931, 48, pp. 507-514.

5. Loewenthal, L. J. A.: A New Cutaneous Manifestation in the Syndrome of Vitamin A Deficiency. *Archives of Dermatology and Syphilology*, November, 1933, 28, pp. 700-708.

6. Frazier, C. N. and Li, H. C.: Vitamin A Deficiency in Man. *Chinese Medical Journal*, October, 1938, 54, pp. 301-314.

7. Frazier, Chester N. and Hu, Chu'Uan K'Uei: Nature and Distribution According to Age of Cutaneous Manifestations of Vitamin A Deficiency. *Archives of Dermatology and Syphilology*, May, 1936, 33, pp. 825-852.

8. Frazier, Chester N.; Hu, Chu'Uan K'Uei; and Chu, Fu-T'Ang: Variations in the Cutaneous Manifestations of Vitamin A Deficiency from Infancy to Puberty. *Archives of Dermatology and Syphilology*, July 1943, 48, pp. 1-4.

9. Loewenthal, L. J. A.: An Inquiry into Vitamin A Deficiency Among the Population of Teso, Uganda, with Special Reference to School Children. *Annals of Tropical Medicine and Parasitology*, October 5, 1935, 29, No. 3, pp. 349-360.

10. Steffens, L. F.; Blair, H. L.; and Sheard, Charles: Photometric Measurements of Visual Adaptation in Normal Adults on Diets Deficient in Vitamin A. *Proceedings of the Staff Meetings of the Mayo Clinic,* November 1, 1939, 14, No. 4, pp. 698-704.

11. Moult, Frank H.: Histopathology of Rat Skin in Avitaminosis A. *Archives of Dermatology and Syphilology,* 1943, 47, pp. 768-777.

12. Sullivan, Maurice, and Evans, Virginia J.: Nutritional Dermatoses in the Rat. VIII. Vitamin A Deficiency. *Journal of Nutrition,* 1943, 25, pp. 319-340.

13. Sweet, Lewis K. and K'Ang, H. J.: Clinical and Anatomic Study of Avitaminosis A Among the Chinese. *American Journal of Diseases of Children,* September, 1935, 50, No. 3, pp. 699-734.

14. Youmans, John B.: The Present Status of Vitamin Deficiencies in Practice. *Journal of the American Medical Association,* January 2, 1937, 108, No. 1, pp. 15-21.

15. Youmans, John B.: Newer Aspects of Vitamin Deficiency Diseases. *American Journal of Tropical Medicine,* May, 1939, 19, pp. 229-241.

16. Lehman, Edward and Rapaport, Howard G.: Cutaneous Manifestations of Vitamin A Deficiency in Children. *Journal of the American Medical Association,* February 3, 1940, 114, No. 5, pp. 386-393.

17. Straumfjord, Jon V.: Lesions of Vitamin A Deficiency. *Northwest Medicine,* July, 1942, 41, pp. 229-233.

18. Straumfjord, Jon V.: Vitamin A: Its Effect on Acne. *Northwest Medicine,* August, 1943, 42, pp. 219-225.

19. Saunders, Thomas S.: Favorable Effects of Vitamin A In a Case of Acne of Long Duration. *Archives of Dermatology and Syphilology,* September, 1944, 50, p. 199.

20. Sandels, Margaret S.; Cate, Helen Dorothy; Wilkinson, Kathleen Perry; and Graves, L. J.: Follicular Conjunctivitis in School Children as an Expression of Vitamin A Deficiency. *American Journal of Diseases of Children,* July, 1941, 62, pp. 101-114.

21. Peck, Samuel M.; Chargin, Louis; and Sobotka, Harry H.: Keratosis Follicularis (Darier's Disease). *Archives of Dermatology and Syphilology,* February, 1941, 43, No. 2, pp. 223-229.

22. Peck, Samuel M.; Glick, Arthur W.; Sobotka, Harry H.; and Chargin, Louis: Vitamin A Studies in Cases of Keratosis Follicularis (Darier's Disease). *Archives of Dermatology and Syphilology,* July, 1943, 48, pp. 17-31.

23. Lester, R. P.: Vitamin Therapy in Relation to Dermatology. *Journal of the Medical Association of Alabama,* December, 1941, 11, pp. 190-197.

24. Carleton, Alice and Steven, David: Keratosis Follicularis. *Archives of Dermatology and Syphilology,* August, 1943, 48, pp. 143-150.

25. Tolmach, Jesse A. and Graham, Thomas N.: Pigmentation of the Skin due to Vitamin A Deficiency. *Archives of Dermatology and Syphilology,* June, 1942, 45, pp. 1156-1163.

26. Goss, Paul: Nummular Eczema. *Archives of Dermatology and Syphilology,* December, 1941, 44, No. 6, pp. 1060-1077.

27. Mackay, Helen M. M.: Vitamin A Deficiency in Children. Part II. Vitamin A Requirements of Babies: Skin Lesions and Vitamin A Deficiency. *Archives of Diseases of Childhood,* June, 1934, 9, pp. 133-152.

28. Mashkilleison, L. N.; Benyamovich, E. B.; Krichevskaya, E. D.; and Shata-

mova, L. V.: The Role of Vitamins in the Pathogenesis and Treatment of Skin Diseases, *American Review of Soviet Medicine,* October, 1945, iii, No. 1, pp. 19-27.

29. Kohn, G.; Milligan, E. H. M.; and Wilkinson, John F.: Levels of Vitamins A and C Nutrition in Glossop School-Children and Effect of Deficiencies on their Physical Condition. *British Medical Journal,* October 16, 1945, ii, pp. 477-481.

30. Crandon, J. H.; Lund, C. C.; and Dill, D. B.: Experimental Human Scurvy. *New England Journal of Medicine,* September 5, 1940, 223, pp. 353-369.

31. Jeghers, Harold: Skin Changes of Nutritional Origin. *New England Journal of Medicine,* May 27, 1943, 228, pp. 678-686.

32. Kruse, H. D.: A Concept of the Deficiency States. The Milbank Memorial Fund *Quarterly,* July, 1942, xx, No. 3, pp. 245-261.

33. Pillat, Arnold: Does Keratomalacia Exist in Adults? *Archives of Ophthalmology,* October, 1929, v, pp. 399-415; The Production of Pigment in Night Blindness, Prexerosis, Xerosis and Keratomalacia of Adults. *Archives of Ophthalmology,* 1933, ix, pp. 25-47.

34. Blackfan, Kenneth D. and Wolbach, S. Burt: Vitamin A Deficiency in Infants. *Journal of Pediatrics,* November, 1933, 3, pp. 679-706.

35. Youmans, John B.; Corlette, Marvin B.; Corlette, Mildred G.; and Frank, Helen: Inadequacy of Conjunctival Smears in the Diagnosis of Slight Vitamin A Deficiency in Adults. *Journal of Laboratory and Clinical Medicine,* April, 1938, 23, pp. 663-670.

36. Kruse, H. D.: Medical Evaluation of Nutritional Status. IV. The Ocular Manifestations of Avitaminosis A, with Especial Consideration of the Detection of Early Changes by Biomicroscopy. *Public Health Reports,* June 27, 1941, 56, No. 26, pp. 1301-1324; and the Milbank Memorial Fund *Quarterly,* July, 1941, xix, No. 3, pp. 207-240.

37. Kruse, H. D.: Detection of Avitaminosis A by Gross and Biomicroscopic Examination of the Conjunctiva. *American Journal of Ophthalmology,* November, 1942, 25, No. 11, pp. 1386-1391.

38. Callison, Elizabeth C.: Consideration of the Adequacy of Biomicroscopy as a Method of Detecting Mild Cases of Vitamin A Deficiency. *Science,* March 6, 1942, 95, pp. 250-251.

39. Kruse, H. D.: Methods of Detecting Mild Cases of Vitamin A Deficiency. *Science,* June 19, 1942, 95, No. 2, pp. 623-624.

40. Berliner, M. L.: Regarding Early Detection of Avitaminosis A by Gross or Biomicroscopic Examination of the Conjunctiva. *American Journal of Ophthalmology,* March, 1942, 25, pp. 302-308.

41. Jolliffe, Norman and Stern, Marvin: Objective Manifestations of Nutritional Deficiency Diseases. *Clinics,* August, 1942, i, No. 2, pp. 282-302.

42. Getz, H. R.: Cited in "Inadequate Diets and Nutritional Deficiencies in the United States." *Bulletin of the National Research Council,* November, 1943, No. 109, p. 32.

43. Nicholls, Lucius and Nimalasuriya, Ananda: Bitot's Spots in Ceylon. *Lancet,* June 24, 1939, I, pp. 1432-1434.

44. Metivier, Vivian M.: Bitot's Spots in Trinidad. *American Journal of Ophthalmology,* September, 1941, 24, pp. 1029-1034.

45. Pett, Lionel Bradley: Riboflavin and Vitamin A in Relation to "Eye Strain." *Canadian Medical Association Journal*, October, 1943, 49, pp. 293-295.

46. Holt, L. Emmet and Najjar, Victor A.: The Clinical Diagnosis of Deficiencies of Thiamine, Riboflavin, and Niacin. *Journal-Lancet*, November, 1943, 63, pp. 366-371.

47. Stern, Martin H.; Wortis, Herman; and Jolliffe, Norman: Peripheral Neuropathy. Evaluation of Sensory Findings. *Archives of Neurology and Psychiatry*, September, 1941, 46, pp. 464-470.

48. Fox ,James C. Jr. and Klemperer, Wolfgang W.: Vibratory Sensibility, A. Quantitative Study of its Thresholds in Nervous Disorders. *Transactions of the American Neurological Association*, 1941, 67, pp. 171-177; *Archives of Neurology and Psychiatry*, October, 1942, 48, pp. 622-645.

49. Shulack, Norman R. and Peters, Michael: Spinal Cord Changes in Avitaminosis. *Bulletin United States Army Medical Department*, 1945, 3, No. 88, pp. 118-120.

50. Keighley, Geoffrey: An Instrument for Measurement of Vibration Sensation in Man. The Milbank Memorial Fund *Quarterly*, January, 1946, xxiv, No. 1, pp. 36-48.

51. Pearson, Gerald H. J.: Effect of Age on Vibratory Sensibility. *Archives of Neurology and Psychiatry*, 1928, 20, No. 3, pp. 482-496.

52. Kruse, H. D.; Sydenstricker, V. P.; Sebrell, W. H.; and Cleckley, H. M.: Ocular Manifestations of Ariboflavinosis. *Public Health Reports*, January 26, 1940, 55, No. 4, pp. 157-169.

Sydenstricker, V. P.; Sebrell, W. H.; Cleckley, H. M.; and Kruse, H. D.: The Ocular Manifestations of Ariboflavinosis. *Journal of the American Medical Association*, June 22, 1940, 114, pp. 2437-2445.

Sydenstricker, V. P.: Clinical Manifestations of Ariboflavinosis. *American Journal of Public Health*, April, 1941, 31, No. 4, pp. 344-350.

53. Sydenstricker, V. P.; Kelly, A. R.; and Weaver, J. W.: Ariboflavinosis, with Special Reference to the Ocular Manifestations. *Southern Medical Journal*, February, 1941, 34, No. 2, pp. 165-170.

54. Tisdall, F. F.; McCreary, J. F.; and Pearce, H.: The Effect of Riboflavin on Corneal Vascularization and Symptoms of Eye Fatigue in R.C.A.F. Personnel. *Canadian Medical Association Journal*, July, 1943, 49, pp. 5-13.

55. Gregory, M. K.: The Ocular Criteria of Deficiency of Riboflavin. *British Medical Journal*, July 31, 1943, 2, pp. 134-136.

56. Fish, Winifrede M.: Acne Rosacea Keratitis and Riboflavin (Vitamin B2). *British Journal of Ophthalmology*, 1943, 27, pp. 107-109. Ocular Rosacea and Ariboflavinosis. *American Journal of Ophthalmology*, 1944, 27, pp. 354-357.

57. Mann, Ida: Ariboflavinosis. *American Journal of Ophthalmology*, March, 1945, 28, No. 3, pp. 243-247.

58. Sydenstricker, V. P.; Hall, W. Knowlton; Hock, Charles W.; and Pund, Edgar R.: Amino Acid and Protein Deficiencies as Causes of Corneal Vascularization: A Preliminary Report. *Science*, February 15, 1946, 103, No. 2668, pp. 194-196.

59. Sydenstricker, V. P.; Hall, W. Knowlton; Hock, Charles W.; and Briggs, A. P.: Corneal Vascularization as a Sign of Dietary Deficiency in the Rat. *Federation Proceedings*, Part II, February, 1946, 5, p. 242.

60. Vail, Derrick and Ascher, K. W.: Corneal-Vascularization Problems. *American Journal of Ophthalmology*, October, 1943, 26, pp. 1025-1044.

61. Scarborough, H.: Circumcorneal Infection as a Sign of Riboflavin Deficiency in Man, with Account of Three Cases of Ariboflavinosis. *British Medical Journal,* November 21, 1942, 2, pp. 601-604.

62. Keys, Ancel; Henschel, Austin F.; Mickelsen, Olaf; Brozek, Josef M.; and Crawford, J. H.: Physiological and Biochemical Functions in Normal Young Men on a Diet Restricted in Riboflavin. *Journal of Nutrition,* 1944, 27, pp. 165-178.

63. Pirrie, A.: *British Journal of Ophthalmology,* 1943, 27, pp. 516-518.

64. McCreary, J. F.; Nicholls, J. V. V.; and Tisdall, F. F.: Further Studies on the Relationship of Corneal Vascularization to Riboflavin Deficiency. *Canadian Medical Association Journal,* August, 1944, 51, pp. 106-110.

65. Boehrer, John B.; Stanford, Charles E.; and Ryan, Elizabeth: Experimental Riboflavin Deficiency in Man. *American Journal of Medical Science,* 1943, 205, pp. 544-549.

66. Williams, Ray D.; Mason, Harold L.; Cusick, Paul L.; and Wilder, Russell M.: Observations on Induced Riboflavin Deficiency and the Riboflavin Requirement of Man. *Journal of Nutrition,* 1943, 25, pp. 361-377.

67. Sandstead, Harold R.: Superficial Vascularization of the Cornea. The Result of Riboflavin Therapy. *Public Health Reports,* November 27, 1942, 57, No. 48, pp. 1821-1825.

68. Machella, Thomas E. and McDonald, P. Robb: Studies of the B Vitamins in the Human Subject. VI. Failure of Riboflavin Therapy in Patients with the Accepted Picture of Riboflavin Deficiency. *American Journal of Medical Science,* 1943, 205, pp. 214-223.

69. Goldsmith, Grace A.: The Incidence and Recognition of Riboflavin and Niacin Deficiency in Medical Diseases. *Southern Medical Journal,* February, 1943, 36, No. 2, pp. 108-116.

70. Ruffin, J. M.: Comment in Research Conference on the Relation of Nutrition to Public Health. New York, Nutrition Foundation, Inc., October 11, 1943, 66 pp.

71. Johnson, Lorand V. and Eckardt, R. E.: Rosacea Keratitis and Conditions with Vascularization of Cornea Treated with Riboflavin. *Archives of Ophthalmology,* 1940, 23, pp. 899-907.

72. Johnson, Lorand V.: Clinical Ocular Conditions Associated with Vitamin —B— Complex Deficiencies. *Archives of Ophthalmology,* November, 1941, 24, pp, 1233-1240.

73. Wise, George: Ocular Rosacea. *American Journal of Ophthalmology,* June, 1943, 26, No. 6, pp. 591-609.

74. Kodicek, J. H. and Yudkin, John: Slit-lamp Microscope in Nutrition Surveys. *Lancet,* December 26, 1942, ii, pp. 753-756.

75. Youmans, John B. and Patton, E. White: The Laboratory Diagnosis of Nutritional Deficiencies. *Clinics,* August, 1942, I, No. 2, pp. 303-345.

76. Sebrell, W. H. and Butler, R. E.: Riboflavin Deficiency in Man. A Preliminary Note. *Public Health Reports,* December 30, 1938, 53, No. 52, pp. 2282-2284.
Sebrell, W. H. and Butler, R. E.: Riboflavin Deficiency in Man (Ariboflavinosis). *Public Health Reports,* December 1, 1939, 54, No. 48, pp. 2121-2131.

77. Smith, Susan Gower; Smith, David T.; and Callaway, J. Lamar: Dysfunction of the Sebaceous Glands Associated with Pellagra. *Journal of Investigative Dermatology,* 1941, 4, pp. 23-42.

78. Rosenblum, Louis A. and Jolliffe, Norman: The Oral Manifestations of Vitamin Deficiencies. *Journal of the American Medical Association,* December 27, 1941, 117, No. 26, pp. 2245-2248.

79. Shields, William P.: Riboflavin Deficiency. Report of a Case in a Child with Cure by Specific Treatment. *New England Journal of Medicine,* August 8, 1940, 223, No. 6, pp. 215-216.

80. Egana, E.; Johnson, R. E.; Bloomfield, R.; Brouha, L.; Meiklejohn, A. P.; Whittenberger, J.; Darling, R. C.; Heath, C.; Graybiel, A.; and Consolanzio, F.: The Effects of a Diet Deficient in the Vitamin B Complex on Sedentary Men. *American Journal of Physiology,* 1942, 137, pp. 731-741.

81. Ellenberg, Max and Pollack, Herbert: Pseudoariboflavinosis. *The Journal of the American Medical Association,* July 4, 1942, 119, No. 10, pp. 790-792.

82. Cayer, David; Ruffin, Julian M.; and Perlzweig, William A.: The Clinical Significance of Glossitis and Cheilosis in Deficiencies of the B Complex. *Southern Medical Journal,* February, 1945, 38, pp. 111-117.

83. Smith, Susan Gower and Martin, David W.: Cheilosis Successfully Treated With Synthetic Vitamin B6. *Proceedings of the Society for Experimental Biology and Medicine,* 1940, 43, pp. 660-663.

84. Machella, Thomas E.: Studies of the B Vitamins in the Human Subject. III. The Response of Cheilosis to Vitamin Therapy. *American Journal of Medical Science,* January, 1942, 203, No. 1, pp. 114-120.

85. Grossman, Maurice: Nutritional Dermatitis Treated with Vitamin B Complex Factors. *Medical Bulletin of the Veterans Administration,* July 1941, 18, pp. 106-107.

86. Kuo, P. T. and Huang, M. S.: Nutritional Stomato-Glossitis. *Chinese Medical Journal,* May, 1941, 59, pp. 430-440.

87. Kruse, H. D.: The Lingual Manifestations of Aniacinosis, with Especial Consideration of the Detection of Early Changes by Biomicroscopy. The Milbank Memorial Fund *Quarterly,* July, 1942, xx, No. 3, pp. 262-289.

88. Sevringhaus, Elmer L. and Kyhos, Emma D.: Reversal of Lingual Atrophic Changes with Nicotinamide Therapy. *Archives of Internal Medicine,* July, 1945, 76, No. 1, pp. 31-33.

89. Fox, F. W.: Ascorbic Acid and the Appearance of Vitamin C Deficiency. *Journal-Lancet,* November, 1943, lxiii, No. 11, pp. 349-353.

90. Kruse, H. D.: The Gingival Manifestations of Avitamonosis C, with Especial Consideration of the Detection of Early Changes by Biomicroscopy. The Milbank Memorial Fund *Quarterly,* July, 1942, xx, No. 3, pp. 290-323.

91. Kyhos, Emma D.; Gordon, Edgar S.; Kimble, Marian S.; and Sevringhaus, Elmer L.: The Minimum Ascorbic Acid Need of Adults. *Journal of Nutrition,* 1944, 27, pp. 271-285.

92. Wintrobe, M. M.: Clinical Hematology. Philadelphia, Lea and Febiger, 1942, 792 pp.

93. Clausen, S. W.: The Influence of Nutrition Upon Resistance to Infection. *Physiological Reviews,* 1934, 14, pp. 309-350.

94. Robertson, Elizabeth Chant: The Vitamins and Resistance to Infection. *Medicine,* 1934, 13, pp. 123-144.

95. Cannon, Paul R.: Antibodies and the Protein-Reserves. *Physiological Reviews*, June, 1942, 44, No. 2, pp. 107-114.

Cannon, Paul R.: Antibody Production and the Anamnestic Reaction. *Journal of Laboratory & Clinical Medicine*, November, 1942, 28, No. 2, pp. 127-139.

Cannon, Paul R.; Chase, William E.; and Wissler, Robert W.: The Relationship of the Protein-Reserves to Antibody Production. I. The Effects of a Low-Protein Diet and of Plasmapheresis upon the Formation of Agglutinins. *Journal of Immunology*, August, 1943, 47, No. 2, pp. 133-147.

Cannon, Paul R.: Food and the War. In MEDICINE AND THE WAR, Taliaferro, W. H., Editor. Chicago, The University of Chicago Press, 1944, pp. 23-39.

Cannon, Paul R.: Protein Metabolism and Acquired Immunity. *Journal of the American Dietetic Association*, February, 1944, 20, No. 2, pp. 77-80.

Cannon, Paul R.: Wissler, Robert W.; Woolridge, Robert L.; and Benditt, Earl P.: The Relationship of Protein Deficiency to Surgical Infection. *Annals of Surgery*, October, 1944, 120, No. 4, pp. 514-525.

96. Gardner, Esther L. and Gardner, Floyd W.: Vitamin A and Colds. *American Journal of Diseases of Children*, 1934, 47, pp. 1261-1264.

97. Tress, Esther M.: Vitamin "A" as a Prophylactic against the Common "Cold" in Groups of Children. *American Journal of Digestive Diseases and Nutrition*, January, 1935, 1, pp. 795-796.

98. Beard, H.H.: The Prophylactic Effect of Vitamins A and D upon the Prevention of the Common Cold and Influenza. *Journal of the American Dietetic Association*, September, 1934, 10, No. 3, pp. 193-199.

99. Cameron, Hazel C.: The Effect of Vitamin A upon Incidence and Severity of Colds among Students. *Journal of the American Dietetic Association*, September, 1935, 11, No. 3, pp. 189-204.

100. Spiesman, Irvin G.: Massive Doses of Vitamins A and D in the Prevention of the Common Cold. *Archives of Otolaryngology*, October, 1941, 34, No. 4, pp. 787-791.

101. Holmes, Arthur D.; Pigott, Madeleine G.; Sawyer, William A.; and Comstock, Laura: Cod Liver Oil — A Five Year Study of its Value for Reducing Industrial Absenteeism Caused by Colds and Respiratory Diseases. *Industrial Medicine*, July, 1936, 5, pp. 359-361.

102. Crampton, C. Ward: Vitamin Aid in the Treatment of Colds. *New York State Journal of Medicine*, January 15, 1944, 44, pp. 162-166.

103. Manwaring, W. H.: Ascorbic Acid vs. The Common Cold. *California and Western Medicine*, June, 1945, 62, No. 6, pp. 309-310.

104. Kay, Leslie L.: Multivitamin Prophylaxis and Therapy in Respiratory Diseases of the Aged. *American Journal of Digestive Diseases*, 1943, 10, pp. 96-98.

105. Glazebrook, A. J. and Thompson, Scott: The Administration of Vitamin C in a Large Institution and its Effect on General Health and Resistance to Infection. *Journal of Hygiene*, January, 1942, 42, No. 1, pp. 1-20.

106. Stone, Florence G.; Bird, Mira S.; and Field, Hazel E.: Vitamins A, B_1, B_2, and D: Effects of Daily Administration of Concentrates. *California and Western Medicine*, February, 1939, 50, No. 2, pp. 125-126.

107. Wright, H. P.; Frosst, John B.; Puchel F.; and Lawrence, Margaret R.: Vitamin A and the Common Cold. *Canadian Medical Association Journal*, 1931, 25, pp. 412-416.

108. Barenberg, L. H. and Lewis, J. M.; Relationship of Vitamin A to Respiratory

Infections in Infants. *Journal of the American Medical Association,* January 16, 1932, 98, pp. 199-202.

109. Hess, A. F.; Lewis, J. M.; and Barenberg, L. H.: Does Our Dietary Require Vitamin A Supplement? *Journal of the American Medical Association,* August 26, 1933, 101, pp. 657-663.

110. Kuttner, Ann G.: The Effect of Large Doses of Vitamins A, B, C, and D on the Incidence of Upper Respiratory Infections in a Group of Rheumatic Children. *Journal of Clinical Investigation,* November, 1940, 19, No. 6, pp. 809-812.

111. Bransby, E. R.; Hunter, J. W.; Magee, H. E.; Milligan, E. H. M.; and Rodgers, T. S.: The Influence of Supplements of Vitamins A, B1, B2, C and D on Growth, Health and Physical Fitness. *British Medical Journal,* January 15, 1944, i, pp. 77-78.

112. Sherman, J. B.: Prophylaxis of the Common Cold. *British Medical Journal,* October 29, 1938, 2, pp. 903-904.

113. Gittleman, Isaac F. and Wiener, Alexander S.: Vitamin A and Infection. *Journal of Pediatrics,* 1935, 7, pp. 81-88.

114. Shibley, Gerald S. and Spies, Tom D.: The Effect of Vitamin A on the Common Cold. *Journal of the American Medical Association,* December 29, 1934, 103, No. 26, pp. 2021-2026.

115. Cowan, Donald W.; Diehl, Harold S.; and Baker, M. D.: Vitamins for the Prevention of Colds. *Journal of the American Medical Association,* December 19, 1942, 120, No. 16, pp. 1268-1271.

116. Sutherland, Robert: Vitamins A and D: Their Relation to Growth and Resistance to Disease. *British Medical Journal,* May 5, 1934, 1, pp. 791-795.

117. Yudkin, John: The Nutritional Status of Cambridge School-Children. *British Medical Journal,* August 12, 1944, ii, pp. 201-205.

118. Diehl, Harold S.: The Common Cold Among College Students. *Journal-Lancet,* November 15, 1934, liv, No. 22, p. 723.

URBANIZATION IN LATIN AMERICA

KINGSLEY DAVIS AND ANA CASIS

AN excellent clue to the economic and social development of an area is the growth of cities. For this there are two reasons. First, the city *reflects* the changes in every sphere of social life. Its growth stems from all the factors that change illiterate agriculturalism to literate industrialism; it is correlated with increased industry and commerce, enhanced education, more efficient birth and death control— in short, with the whole process of modernization. Second, the city is a *source* of change in its own right. It is a diffusion center for modern civilization, providing a milieu in which social ferment and innovation can take place. City expansion therefore helps to determine as well as reflect the trend toward more modern conditions.

The present paper, based mainly on analysis of census data, attempts to relate the growth of cities to regional differences and problems in Latin America. Part I, "The Growth of Cities," considers the rate of urban as against rural population growth, the development of cities of different size, and the causes and consequences of urban expansion. Part II, "The Characteristics of City Populations," discusses the age, sex, fertility, literacy, and other differentials as between country and city and as between various classes of city. The entire study is meant as a contribution to Latin American demography and sociology.

Necessarily the treatment cannot be complete, because the data are not available for all areas or for all periods, and when available, are sketchy and unstandardized. It requires a great deal of labor and often a process of estimation to make the statistics com-

[1]From the Office of Population Research, Princeton University, where the first author is a member of the staff and the second a Milbank fellow. The paper is an outgrowth of a thesis of the same title done by Miss Casis. Though the thesis was for the Master's degree at Syracuse University (1945), the work for it was done in the Office of Population Research under the immediate supervision of Dr. Davis. It was limited to four countries. The present work expands the area covered to as much of Latin America as possible, and is based on further research by both authors.

Table 1. Per cent of population in cities by size class.[2]

parable from one region to another and from one time to the next.

Part I. The Growth of Cities

The Degree of Urban Concentration. In comparison with more industrialized areas, the Latin American countries do not seem, at first glance, to be highly urban. In the United States in 1940, for example, the percentage of persons living in places of more than 5,000 inhabitants was 52.7, and for Canada 43.0, whereas for most of Latin America it was only 27.1 (Table 1).[2] But when one realizes that the difference in urban concentration is very much smaller than the difference in industrial development,[3] and that, as compared with nearly all other areas the Latin American countries have a very much smaller average density, the percentage of urban dwellers in the countries to the south begins to look fairly high. Indeed, it seems to us that in view of its retarded industrialization, Latin America is urbanized to a surprising degree. In other areas the growth of cities has arisen from large-scale industrial development, but in Latin America it has come more from non-industrial causes.

Table 1 gives for each country the percentage of the population living in cities of various size limits, with an unweighted average for each region. Column 6 of the table provides a rough index of urbanization, obtained by averaging the percentages in the preceding four columns. This index gives greater weight to

[2]The countries included in Table 1 do not embrace quite all of the Latin American region. They do cover 95.4 per cent of the total area and 94.5 of the total population. The areas omitted (mainly Paraguay, British Honduras, the Guianas, and most of the Caribbean islands) are undoubtedly more rural than those included, but since the parts omitted are very small in comparison to the total, the error introduced by this factor cannot be very great. The subregion most poorly covered is the Caribbean, where our sample embraces only 25.2 per cent of the area and 58.0 per cent of the population. Only in the case of this subregion is there a likelihood of serious misrepresentation.

[3]"One may conclude that in general the average per capita income in Latin America cannot be much more than $100 per year and is probably less. The national income of all Latin America might then run to about $10 to $15 billion as compared with a current [1944] income of $155 billion in the United States." Harris, Seymour E.: Economic Problems of Latin America. New York, McGraw-Hill, 1944, p. 4.

Table 1. Per cent of population in cities by size class.[1]

Region and Country	Year	In Cities 5,000+ Per Cent	In Cities 10,000+ Per Cent	In Cities 25,000+ Per Cent	In Cities 100,000+ Per Cent	Index[a]	Per Cent in the Largest City
Latin America—Total Sample		27.1	23.6	19.0	13.4	20.8	8.2
ABC Area		42.7[d]	39.6	34.0	25.1	35.4	18.4
Uruguay	e. 1941	55.8	52.0	44.4	32.4	46.2	32.4
Argentina[f]	e. 1943	48.9	46.8	42.7	34.0	43.1	18.5
Chile	c. 1940	44.8	41.1	34.3	23.1	35.8	19.0
Brazil	c. 1940	21.3	18.4	14.6	11.0	16.3	3.8
Paraguay[b]							
Western South America		22.2	18.6	13.0	8.5	15.6	6.1
Ecuador	e. 1944	35.5	29.6	13.2	10.7	22.3	5.2
Venezuela[g]	c. 1936	22.0	17.7	13.0	9.0	15.4	5.8
Peru[g]	c. 1940	18.1	15.4	11.6	7.4	13.1	7.4
Bolivia[f]	e. 1942	16.5	15.3	15.3	8.5	13.9	8.5
Colombia[g]	c. 1938	19.0	15.2	12.1	7.1	13.3	3.7
Middle America, including Mexico		20.0	15.6	12.3	9.6	14.4	8.5
Panama[g]	c. 1940	26.2	24.7	24.7	17.7	23.4	17.7
Mexico[g]	c. 1940	27.5	21.9	16.8	10.2	19.1	7.4
Nicaragua	e. 1941	26.0	20.6	15.6	—	20.7	9.4
El Salvador	e. 1942	20.4	14.7	8.1	5.6	12.2	5.6
Costa Rica[f]	e. 1943	17.4	12.1	10.6	—	13.4	10.6
Guatemala	c. 1940	13.2	8.4	6.0	5.0	8.2	5.0
Honduras	c. 1940	9.5	6.7	4.0	—	6.8	4.0
Caribbean, Major Antilles		26.8	23.6	17.6	11.3	19.8	9.7
Cuba[g]	c. 1943	38.8	35.5	28.8	18.8	30.5	13.8
Puerto Rico[g]	c. 1940	25.8	21.2	15.2	9.0	17.8	9.0
Dominican Republic	e. 1944	15.8	14.1	8.8	6.1	11.2	6.1
Haiti[b]							
Jamaica[b]							
North America		47.8	43.1	36.4	25.9	38.3	6.8
United States[g]	c. 1940	52.7	47.6	40.1	28.8	42.3	5.7
Canada[g]	c. 1941	43.0	38.5	32.7	23.0	34.3	7.8
European Countries[h]							
Great Britain	c. 1931	81.7[c]	73.6	63.1	45.2	65.9	20.5
Germany	c. 1939	57.4[c]	51.7	43.5	31.8	46.1	6.3
France	c. 1936	41.7[c]	37.5	29.8	16.0	31.2	6.8
Sweden	c. 1935	37.1[c]	33.4	27.0	17.5	28.7	1.0
Greece	c. 1937	33.1[c]	29.8	23.1	14.8	25.2	7.0
Poland	c. 1931	22.8[c]	20.5	15.8	10.7	17.4	3.6
Non-European Countries[h]							
India	c. 1931	10.4	8.5	5.8	2.7	6.8	0.3
India	c. 1941	12.3	10.5	8.1[e]	4.2	8.8	0.5
Australia	c. 1933	[b]	[b]	73.8	45.5	[b]	18.4
Japan	c. 1935	64.5	45.8	36.8	25.3	43.1	8.5
Egypt	e. 1939	[b]	27.0	19.7	13.2	[b]	8.2

[a] The index of urbanization was computed by adding the percentages in the previous four columns and dividing by four.

[b] Figures not available to the authors.

[c] Percentages based on data from a census are designated by a "c" in front of the date of the census.

[d] All regional percentages are unweighted averages, obtained by adding the percentages of the component countries and dividing by the number of countries.

[e] Percentages based on estimated population figures are designated by an "e" in front of the date of the estimate.

[f] Data on cities incomplete.

[g] Except for those countries otherwise designated, the population figures on which the percentages rest were taken from the *Handbook of Latin American Population Data* (Washington, D.C.: Office of Inter-American Affairs, 1945).

[h] Population figures were taken from census, yearbook, or other government publications.

[i] Figures taken from United States Department of State, Division of Geography and Cartography, *Europe (without U.S.S.R.): Cities of 10,000 Population and Over by Size Categories, circa 1930*, No. 108, April 5, 1944. The percentage for 5,000+ in each case was estimated by us by assuming that the ratio between the percentage in cities 5,000+ and the percentage in cities 10,000+ was the same as the average ratio in the United States and Canada.

the larger places and thus expresses the depth, or profundity, of urban concentration.[4] It follows rather closely the percentage of persons in cities of 25,000 or more.

By these figures, the most urbanized countries to the south are Uruguay, Argentina, Chile, Cuba, and Panama, in the order named.[5] The first three, strangely, are more urbanized than France (with 37.5 per cent in cities 10,000-plus); the first four, more urbanized than Sweden (with 33.4 per cent in cities 10,000-plus).

As might be expected, the various regions show sizable differences in the proportion urban. The so-called ABC area of South America has a high degree of urban concentration—an index figure of 35.4 as compared with the North American figure of 38.3[6]. In fact the concentration in the first three countries of the ABC area — Uruguay, Argentina, and Chile — exceeds that of Canada and comes close to that of the United States, although they are far less industrialized than these two countries.

The next most urbanized region is the Caribbean. Doubtless

[4]It should be borne in mind that the average density in most of these countries is low. Argentina, for example, has only 5 persons per square kilometer, whereas England has 202. A country with as dense a population as England must necessarily have a considerable degree of urbanization, whereas there is nothing in the density of Argentina that would require urbanization.

[5]It should be stressed that in a number of cases the urban percentages are approximate only. Since Argentina has not had a census since 1914 and Uruguay has not had one since 1908, the data are deficient both in the numerator and the denominator of the fraction by which the percentages are obtained. In the case of Argentina there have been some special censuses of particular cities and provinces, so that the percentages should be reasonably approximate. Uruguay is more questionable, although observers generally affirm that it is a very urbanized country. The data for Chile, Cuba, and Panama are based on censuses.

[6]The regional averages given in Table 1 are obtained by adding the percentages for the countries of the region and dividing by the number of countries. This has the advantage of showing the situation prevailing in the average country of the region, but if the region is viewed as a unit in itself, then the average should be obtained by weighting the percentages according to the population of each country. When this is done, the following averages are obtained for each region.

	Cities 5,000+	Cities 10,000+	Cities 25,000+	Cities 100,000+	Index	Largest City
ABC Area	30.5	27.7	23.5	17.9	24.9	9.2
Western S. America	20.8	17.4	12.7	8.1	14.7	5.9
Middle America	24.3	19.0	14.4	8.4	16.5	7.2
Caribbean	30.7	27.5	21.3	13.8	23.3	11.0

the whole of this sector is not urbanized to the degree indicated by the only three Caribbean countries included in Table 1, but the addition of such places as Jamaica, Haiti, Trinidad, Guadaloupe, Martinique, and Curacao would not bring the region down to the level of either Western South America or Middle America. Cuba stands out in this region with an index of 30.5, which is quite remarkable for a country that is almost purely agricultural. Of course the Caribbean is by far the most densely settled part of the Western hemisphere, with the exception of parts of the United States. In an economy based primarily on the export of raw materials and the importation of manufactured goods by boat, as is the case in Latin America, an island has (in relation to the size of its hinterland) the advantage of maximum exposure to water transport. In the history of Latin America the islands were the first areas to be fully exploited, and their seaport cities grew accordingly. Today the Caribbean islands are the only places already faced with a serious population problem, and they are places where urbanization, in the sense of concentration of people, has gone ahead out of all proportion to the industrial base.

The other two regions—Western South America and Middle America (including Mexico)—have a very similar degree of urbanization. For the most part they are countries with exceedingly mountainous terrain, with large Indian populations, and with inaccessible hinterlands. In view of these characteristics the degree of urbanization, though the lowest in Latin America, is surprisingly large. Ecuador, with nothing but population estimates, is uncertain; the same is true of Bolivia and Nicaragua. Panama, by virtue of its proximity to the Canal Zone, is in a special category. Mexico, the most industrialized country of the two regions, also has the highest degree of urbanization, if only those nations having accurate census information (except Panama) are considered.

The last column in Table 1 gives for each country the percentage of the total population found in the largest city.[7] It is interesting to note that on the average the Latin America countries rank above the United States and Canada in this respect. Also, the ABC area is again outstanding, with the Caribbean, Middle American, and Western South American regions following in the order named. Finally, every one of the largest cities in each country is at the same time the political capital of the nation, whereas this is not true of the United States, Canada, India, or Australia. The fact that each country's largest city is invariably the capital and generally holds a sizable percentage of the total population may be an accident, but it is more probably an integral feature of Latin American social structure.

In the entire Latin American region there are twenty cities with more than 200,000 inhabitants, according to figures for 1940 or thereabouts. Of these twenty, the greatest number (13) are to be found in the ABC area, the next largest number (4) in the Western South American area, the next largest number (2) in the Middle American area, and the least number (1) in the Caribbean. (Table 2.)

Nearly all of the twenty largest cities are located either on the coast or on navigable waterways. This fact is not unusual, but the greater part of Latin America is distinguished by very poor communication between city and hinterland. Water-borne transport predominates over rail and highway transport, whereas the reverse is true in most industrialized countries. This fact gives a peculiar orientation to Latin American cities. They tend to face outward toward other countries—even toward other continents—rather than inward toward their own hinterland.

Figure 1 gives, for eight countries with recent and trustworthy census statistics, the percentage of the population living in vari-

[7] This figure is not included in the urbanization index. The largest city does *not* embrace the metropolitan area. In fact, the metropolitan areas have been left out of account in this table entirely. For their treatment see below, especially Table 3.

ous size classes of city above 10,000, and in the rest of the country. The major difference between the most urbanized and least urbanized countries lies in the 100,000-plus class. It is in the large cities that urban concentration is having its main effect.

In nearly all cases we have taken the definition of the city's size and area from the censuses or official estimates. The Latin Ameri-

Table 2. Twenty largest cities in Latin America by rank, country, and region, about 1940.[1]

City and Size Class	Population[a]	Country	Region
1,000,000+			
Buenos Aires*	2,567,763	Argentina	ABC Area
Rio de Janeiro	1,563,787	Brazil	ABC Area
Mexico City	1,448,422	Mexico	Middle America
São Paulo	1,269,319	Brazil	ABC Area
500,000–1,000,000			
Santiago	952,075	Chile	ABC Area
Montevideo*	708,233	Uruguay	ABC Area
Habana[2]	659,883	Cuba	Caribbean
Rosario*	521,210	Argentina	ABC Area
Lima[3]	520,528	Peru	Western S.A.
200,000–500,000			
Avellaneda*	399,021	Argentina	ABC Area
Cordoba*	339,375	Argentina	ABC Area
Recife	327,753	Brazil	ABC Area
Bogota	325,658	Colombia	Western S.A.
La Paz[4]	301,450	Bolivia	Western S.A.
Salvador	293,278	Brazil	ABC Area
Caracas[5]	269,030	Venezuela	Western S.A.
Pôrto Alegre	262,678	Brazil	ABC Area
La Plata*	256,378	Argentina	ABC Area
Guadalajara	229,235	Mexico	Middle America
Valparaiso	209,945	Chile	ABC Area

[a] Except for places marked by an asterisk, the figures came from census reports.

[1] The Office of Inter-American Affairs: Handbook of Latin American Population Data. Washington, D.C., January, 1945.

[2] República de Cuba. Dirección General del Censo: Informe General del Censo de 1943. Habana, P. Fernández y Cía, S. en C., 1945, p. 84.

[3] República del Perú. Ministerio de Hacienda y Comercio. Dirección Nacional de Estadística: Censo Nacional de Población y Ocupación, 1940. Lima, Noviembre, 1944, Vol. 1, p. 36.

[4] H. Alcaldía Municipal de La Paz. Dirección General de Estadística: Censo Demográfico de la Ciudad de La Paz, 1942. La Paz 1943, p. 12.

[5] Estados Unidos de Venezuela. Ministerio de Fomento. Dirección General de Estadística: Anuario Estadístico de Venezuela, 1943. Caracas, 1938, p. 77.

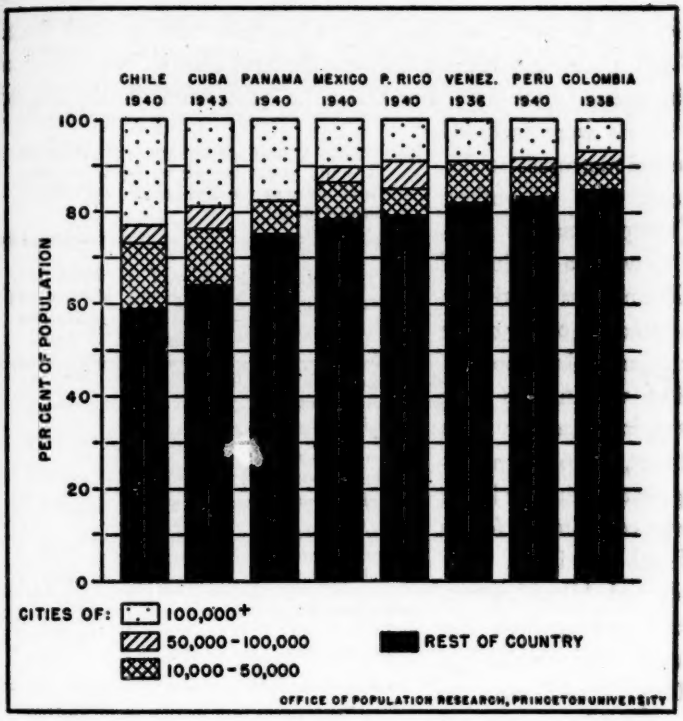


Fig. 1, Per cent of population living in various size classes of city above 10,000, and in rest of country. Selected countries.

can publications, however, do not always specify the exact boundary or area of the city. In general it seems that the city is narrowly rather than broadly defined—that is, there is a suburban population around the city that is not included. This means that we have been dealing with cities proper, rather than with metropolitan districts. The question is raised, then, as to what size the metropolitan areas may have.

For Chile the census gives figures for Greater Santiago in 1930. For Puerto Rico, Bartlett and Howell give the municipali-

ties that form the boundary of the San Juan Metropolitan Area.[8] For Caracas and Mexico City the Federal District was taken as the metropolitan area. For Cuba the cities immediately around Havana were included in the metropolitan district. For all others (except Panama) a circle with a radius of fifteen miles was drawn around the center of the city, and all the population within this area was included. In most cases, a person acquainted with the locale was consulted before a final decision was reached. All told, seventeen metropolitan districts were worked out. They would seem to be roughly accurate; if anything, they exaggerate rather than minimize the metropolitan population.

Table 3. Suburban population as percentage of entire population of metropolitan areas, Latin America (around 1940) and United States (1940).[1]

Size of Metropolitan Area	Number of Metropolitan Areas Included	Percentage of Population in Suburban Part
1,000,000+		
Latin America	4	12.5
United States	11	35.2
500,000–1,000,000		
Latin America	4	7.7
United States	11	32.5
200,000–500,000		
Latin America	7	23.2
United States	37	26.9
100,000–200,000		
Latin America	2	13.6
United States	37	30.7

[1] The figures for Latin America were derived from censuses and official estimates by procedures described in the text. The countries included, and the number of metropolitan districts dealt with, are Argentina (1), Brazil (2), Chile (2), Colombia (3), Cuba (1), Mexico (3), Panama (1), Peru (1), Puerto Rico (1), Uruguay (1), and Venezuela (1). The figures for the United States were derived from U. S. Bureau of the Census, Census of 1940, Vol. I, NUMBER OF INHABITANTS, pp. 61-65, but only those districts were used which were also metropolitan districts in 1930.

Our hypothesis was that the proportion living in the suburban area would be smaller in Latin America than in more industrialized regions. This turned out to be the case. Table 3 compares the Latin American percentages with those in the United States. Apparently the trend toward suburbanization has not gone so

[8] Bartlett, Frederic P. and Howell, Brandon: THE POPULATION PROBLEM IN PUERTO RICO. Government of Puerto Rico: Planning, Urbanizing, and Zoning Board, 1944, p. 47.

far in the countries to the south, doubtless because of less developed transportation, poorer communication, greater poverty, and the preference of Latin Americans for the central city.

The greatest percentage of the metropolitan population living in the suburbs is found in the following districts:

Puebla (Mexico)	43.6
San Juan (Puerto Rico)	43.3
Medellin (Colombia)	33.6
Havana (Cuba)	21.7
Caracas (Venezuela)	20.3
Mexico City (Mexico)	17.6
Buenos Aires (Argentina)	17.3
Panama City (Panama)	15.3

It should be borne in mind that we have only a sample of such districts, and that the methods of determining their population are crude. Nevertheless, the conclusion seems justified that although urban concentration has gone far in Latin America, the

Table 4. Growth of population in rural areas and in various classes of city, five countries combined,[1] 1910-1940.

Period	Average Annual Rate of Growth (Per Cent)			
	Rural	Urban		
		Places 2,500+	Cities 10,000+	Cities 100,000+
1910–1920[a]	1.24	2.71	3.15	
1920–1930[b]	0.97	3.03	3.34	
1930–1940[c]	1.43	2.87	2.93	3.20

[a] In not all cases did the census dates coincide exactly with the periods specified. The first period for Chile was 1907-1920, and for Cuba 1907-1919. In such instances the average annual rate of growth for the period covered by the censuses was assumed to apply to the period mentioned in our table. Also, city boundary changes could not be taken into account.
[b] Cuba, 1919-1931.
[c] Cuba, 1931-1943.
[1] Assembled from census data for the following countries: Chile, Cuba, Mexico, Panama, Puerto Rico. For cities 100,000+ Panama drops out because it had no cities of this size in 1930.

metropolitan tendency has not gone very far. The process of suburbanization should become more prominent in the near future.

The Rate of Urban Growth. When one turns to the history of the urban concentration, one finds that the growth of cities in Latin America has been rapid and that it shows no sign of slowing down. In five countries with available data (Chile, Cuba, Mexico, Panama, and Puerto Rico), the urban population (persons in places of more than 2,500) is growing on an average about twice as fast as the rural population (Table 4). Furthermore, the larger the class of city the faster the growth, for the population in places of 10,000 and over is gaining on the 2,500-and-over class, and the population in places 100,000 and over is apparently gaining over all the rest. Figure 2 seems to indicate that the cities between 10,000 and 50,000 are not growing any faster than the general population, but this may be merely a vagary of the particular sample. There can be no doubt that the cities of 50,000 and over are growing at a far more rapid pace than the rest of the population. "Between 1920 and 1940, the population of Brazil increased 36 per cent and the population of the 22 cities for which a 1920 figure is obtainable increased 61 per cent. For the same period, the corresponding per cents for Chile were 34 and 69; for Colombia between 1918 and 1938 they were 49 and 126."[9] The general population of the Latin American countries is growing at an exceedingly fast pace, yet the cities are growing even faster, and the larger cities are growing with phenomenal speed.

In studying the expansion of cities of different size, one should keep in mind two distinct ways of measuring urban growth. One—the class method (used above)—traces the percentage of the population in each class of city from one census to the next, ignoring the shifting of particular cities from one class to an-

[9]Dunn, Halbert L. *et al.*: Demographic Status of South America. ANNALS OF THE AMERICAN ACADEMY OF POLITICAL AND SOCIAL SCIENCE, 237, January 1945, p. 25.

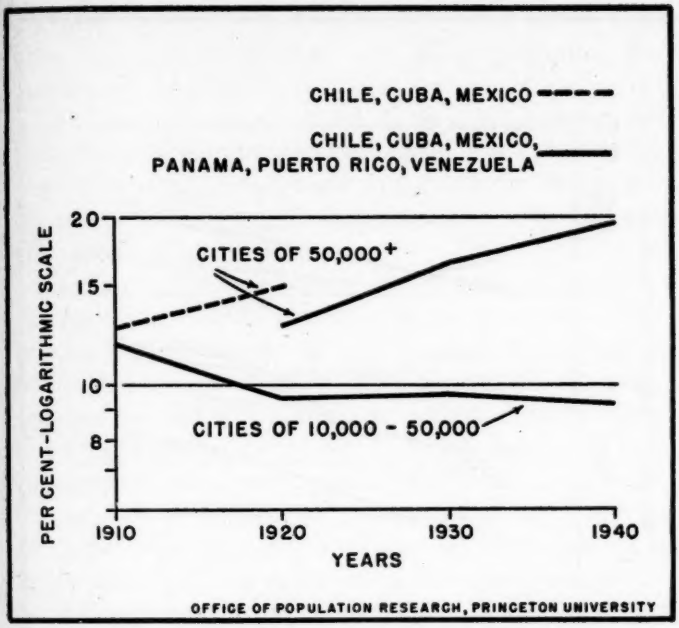


Fig. 2. Per cent of total population living in cities of two size groups. Selected countries.

other. The other—the city method—begins with particular cities and traces their subsequent expansion, ignoring what classes they may later fall into or what cities may later enter the same class. The first measure shows what is actually happening to the population in terms of its distribution by size of city. The second shows what is happening to specific cities as a result of their initial size differences. Since each method supplies an important and complementary kind of information, both are employed in the present study. Having used the first method already, we are now ready to apply the second.

Figure 3 shows for six countries the percentage of the total population living, during 1910-1940, in cities that *were* 20,000 or

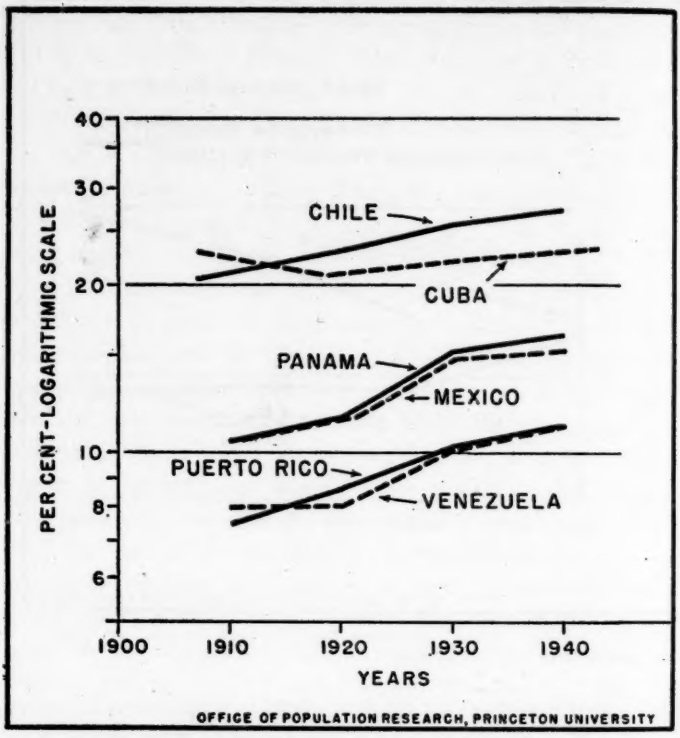


Fig. 3. Per cent of total population, 1910-1940, in cities that *were* 20,000 and over at beginning of period.

over at the initial date. Without exception these particular cities have grown faster than the general population, but it is worth noting that the rate of increase seems inversely correlated with the initial percentage. Those countries (Chile and Cuba) which had at the beginning the highest per cent living in these cities, showed a slower rate of growth of concentration in these cities throughout the period than did the countries that had a much smaller per cent to start with. This suggests that perhaps the older cities that had the highest proportion of people have not

increased their percentage of the country's population as fast as those that did not begin with such a high proportion, but the data are not conclusive.

The Causes of Urban Growth. If the urban concentration in Latin America has already gone beyond that called for by the stage of industrial development, and if it is destined to increase still more in the future, the next question is why such striking urbanization is taking place.

Speaking first in purely demographic terms, we can say that the cause of rapid urban growth is *not* a superior natural increase in cities. In all probability the natural increase of the urban population is less than that of the rural population. Without exception, wherever the data are available, the ratio of children to women in the reproductive ages is lower in the city than in the country. Furthermore, when vital statistics are sufficiently reliable for comparisons to be made (as in Argentina, Chile, and Puerto Rico), the urban birth rate is substantially lower than the rural. At the same time, the death rate in the cities is not sufficiently lower than that in the country to balance the inferior fertility; in fact in some cases the urban mortality may be higher.[10]

We must attribute the growth in urban concentration mainly to the other demographic factor—migration. The importance of this factor is shown by the age distribution of the cities. The combined data for six countries (Chile, Colombia, Mexico, Panama, Puerto Rico, and Venezuela) show that the cities 10,000 and over had 55 per cent of their population in the ages 15-49, whereas the rest of the population had only 47 per cent in these ages.[11] Statistics on rural-urban migration in Latin American countries are discouragingly scarce, but one or two cases may indicate the general situation. In the Venezuelan capital, Caracas, according to the 1936 census, 47.8 per cent of the population were born out-

[10]The subject of rural-urban vital statistics is discussed in Part II.

[11]A part of the difference is probably accounted for by differential fertility, but not all of it.

side the City; and in the Federal District 43.2 per cent were born outside the Federal District, a figure which, by 1941, had risen to 50.8. In 1921 the Federal District of Mexico, according to census returns, had 44.1 per cent of its population born outside the District, and in 1930, 50.8 per cent. In 1940 in Peru, the wholly urban province of Callao had 51.4 per cent of its population born outside the province, and the Department of Lima, 67.6 per cent urban, had 35.7 born outside the Department. It is true, too, that the foreign-born population of Latin America is mainly concentrated in the cities. In Panama, for instance, the two cities of Panama and Colon contained in 1940, 72.5 per cent of the total foreign-born population of the country; indeed, more than 23.5 per cent of these cities' inhabitants were foreign-born. In Buenos Aires, according to the census of 1936, the percentage of foreign-born was 36.1, which was much higher than the proportion of foreign-born (estimated at about 20 per cent) in the total country.[12]

But why the migration to the cities? This question raises a paradoxical issue. If, as maintained above, the urbanization has gone beyond its industrial base, compared with other areas, how does it happen that there is considerable rural-urban migration? What is the incentive? The answer seems to lie in Spanish and Portuguese institutions on the one hand coupled with the Latin American environment on the other.

Progress in Latin America did not begin spontaneously or indigenously. Instead, coming as a foreign, ocean-borne intrusion, it began on the coastal borders, where the Europeans first settled and where water transport was available. This might have have been a prelude for gradual penetration and settlement of the interior, and so it was in a sense. But the Central and South American land masses were tropical or semi-tropical, moun-

[12]Bunge, Alejandro E.: UNA NUEVA ARGENTINA. Buenos Aires, Guillermo Kraft, 1940, pp. 116, 141.

tainous or jungly, excessively wet or dry, and peopled by hostile or at least alien peoples. The conditions offered formidable barriers to settlement, and the Spaniards hardly had hard work in mind. As a consequence, the interior was not developed along the lines of homestead farming, but was given to large landowners (*encomenderos*) who used native or slave labor and aimed at getting out from forest, field, or mine as quickly as possible a commercial product for foreign shipment. The market lay across the ocean. The city, usually a port, was the necessary nexus, without which the interior would be worthless.

The interior, inaccessible and undeveloped, had little of culture or convenience to offer. It was remote from the center of civilization (Europe), and from the cities through which European influence filtered. Nobody wanted to stay there any longer than necessary. To live in the city was every man's dream. Persons who owned enough land in the interior lived in the city, where they formed a class of absentee landowners, educating their children abroad, doting on Europe, and in general neglecting the interior from which their wealth came. The existence of this class also drew to the cities a numerous body of retainers giving service to the rich.

As time went by the interior improved very little. Absentee ownership, the use of slave or peon labor, the lack of local industry and local demand all impeded agricultural progress, despite the effort to raise commercial crops. In the absence of mechanization, human labor had to bear the burden of agricultural production.[12] The competition with more mechanized and accessible agriculture in other continents, plus the peon system, drove rural "wages" down to virtual subsistence. To the agricultural worker

[12]There were in 1920, according to the census, some 141,000 plows in all of Brazil. There were six whole states with fewer than 100 plows each, and on the average only 15 per cent of Brazilian farmers possessed this elementary tool. There were 435 agricultural workers per plow. "Recent trips throughout the nation convince me that the same is true today." Smith, T. Lynn: BRAZIL: PEOPLE AND INSTITUTIONS. Baton Rouge, University of Louisiana Press, 1946, pp. 51-53.

almost any city wage looked attractive, and he filled the need of the aristocracy in the towns for "unspoiled" menial labor. There was thus a stimulus to cityward migration for both the laboring and landowning classes.

The emphasis upon urban dwelling among the wealthy meant that living conditions in cities were improved greatly, whereas little improvement was made in the country. Sanitation, education, utilities, and amusements were fostered in the city, but not elsewhere. The resulting gulf between city and country, still noticed by travelers and amply documented in rural-urban statistics, served to reinforce the initial preference for the city as a place to live. The idea of a quiet home in the country, far from the urban crowd—an ideal dear to the Anglo-Saxon—was not prominent in the Latin American mind.

The growth of cities was also fostered by political factors. Despite an expressed preference in the leading republics for federalism and decentralization, the Latin American countries have usually had centralized governments. Since everything, including economic advantage, political patronage, and cultural support revolved about politics, the capitals became the national nerve-centers. It is therefore no accident that in every Latin American country the largest city is also the capital.

In short, the rural-urban migration that has given rise to unusual urbanization has not been due to heavy industrialization, but rather to the peculiar institutions of the Spaniards and Portuguese and the environmental conditions in their part of the new world. Today there is the prospect that industrialization will play a greater role, and that some of the Latin American nations will carry urban concentration still further.

The Case of Argentina. The most urbanized of the larger republics, Argentina is experiencing a "de-peopling of the pampas." In 1930 the rural population (persons in places of less than 1,000) was estimated to be 3.58 million; by 1938, 3.32 million. (Figure

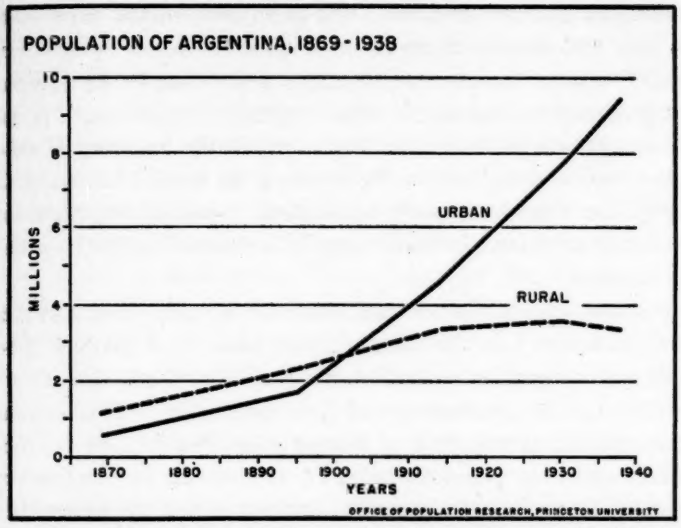


Fig. 4. Growth of rural and urban population in Argentina. (*Rural* is defined as places having less than 1,000 inhabitants.) Data from Bunge, *op. cit.*, p. 158.

4). In percentage terms, the rural population dropped during this time from 32 to 26 per cent of the total population.[24] Since 1938 the rural population has probably declined still further, both in absolute and in percentage figures.

This rural decline bespeaks a huge rural-urban migration. Between 1930 and 1939, for example, an estimated 260,000 rural dwellers, or 7.3 per cent of all such dwellers, migrated to the towns.[25] The rural exodus, plus foreign immigration, explains the phenomenal expansion of the urban population—an expansion that has exceeded the rate of rural growth since 1895.

It is primarily the larger cities that have gained. The census of 1914 showed 24 per cent of the total population living in cities of 100,000-plus, while estimates for 1943 place the figure at 34 per cent. "Between 1914 and 1943 the population of Argentina in-

[24] Bunge: *op. cit.*, pp. 156-158.
[25] *Ibid.*, p. 165.

creased by 74.6 per cent, while the population of the cities that in 1914 had 100,000 or more inhabitants increased by 106 per cent."[16] Greater Buenos Aires contains today close to 3.4 million persons, or above one-fourth of the Argentine population. It is, as Preston James points out, the largest city in the Southern Hemisphere and is second only to Paris among the world's Latin cities. Truly, for a predominantly agricultural country, Argentina is extremely urbanized. Its closest parallel is Australia, which is even more urban.

It is the organization of agriculture on the one hand, and the birth of industry on the other, that explains the Argentine phenomenon. Argentina resembles many another Latin American country in the concentration of land ownership.[17] It has been estimated that almost half of Buenos Aires Province, by far the richest and most populous province, is controlled by not more than 3,500 people, or one-tenth of one per cent of the provincial population; and most other parts of the country are similarly controlled. Large *estancias* and *latifundios* dominate the agricultural scene. The holdings are organized along two different lines. Some of them (about 38 per cent) are run by their owners or by salaried managers; others (about 62 per cent) are cultivated by tenants, sharecroppers, etc.[18] The class of persons who own their own farm and work it with their own hands is extremely small. Most of the big landholders are absentee owners—many of them being simply stock-holders in agricultural corporations.

Though resembling her neighbors in the concentration of land-

[16]Direccion del Censo Escolar de la Nacion: "La distribucion por zonas de la poblacion argentina" (Buenos Aires, 1945, mimeographed), p. 20. All demographic figures for Argentina since 1914 are approximate only, with the exception of those derived from provincial censuses, but it is hard to reconcile our findings with the statement of Preston E. James that "in 1939, approximately two thirds of the population was in cities of more than one hundred thousand." LATIN AMERICA. New York, Odyssey Press, 1942, p. 281.

[17]Notable exceptions: Haiti, El Salvador, Costa Rica.

[18]Weil, Felix J.: ARGENTINE RIDDLE. New York, Latin American Economic Institute and John Day Co., 1944, pp. 94-95, 87-89.

ownership, Argentina differs from them in the degree to which her estates are mechanized and the need for manpower thus reduced. The equipment, even in the case of large estates, is often not owned by the cultivators; rather it is leased by the day from machine-renting enterprises. Moreover, livestock raising, which requires a relatively small amount of labor, has recently regained its historical dominance over other agricultural activities. The net effect of mechanization and livestock raising has been to reduce the amount of labor needed. Bunge points out that the per capita product of the agricultural population is in Argentina approximately four times what it is in France.[19] Carl C. Taylor has given a graphic account of the labor force of a cattle *estancia.* This *estancia,* covering 50,000 acres, grazing about 32,000 head of livestock, and grossing approximately $300,000 per year, had a permanent working population of 72 persons.[20]

One might think that agricultural mechanization would make rural wages high. But such is not the case in Argentina, because the agricultural proletariat, as against the politically dominant landowning class, has little bargaining power on the *estancia.* It seems generally agreed that rural labor in Argentina is poorly paid and poorly housed, insecure and extremely mobile. If we add that the system of rural credit favors larger holders, and that the tendency toward concentration of ownership is increasing rather than decreasing, it becomes clear why Argentine agriculturalists should desire to leave the land.

At the same time, Argentine industry, concentrated in the cities, has been growing at a fast pace for several decades. It has drawn hard-pressed laborers and tenants from the pampas like a magnet. Thus there have been two forces—agriculture pushing and industry pulling—which have carried huge numbers to the cities.

[19] *Op. cit.,* pp. 162-163.

[20] Taylor, Carl: Rural Locality Groups in Argentina. *American Sociological Review,* 9, April, 1944, p. 163.

The cities, in turn, are having a noteworthy effect on the country. Argentina is the first Latin American country to give promise of having a static population. As Figure 5 shows, the birth rate has been steadily declining as the country has become more urban. On the strength of this trend, Bunge has predicted a maximum population of only 13.7 million for Argentina (without immigration) by 1958, after which he believes it will slowly decline.[21]

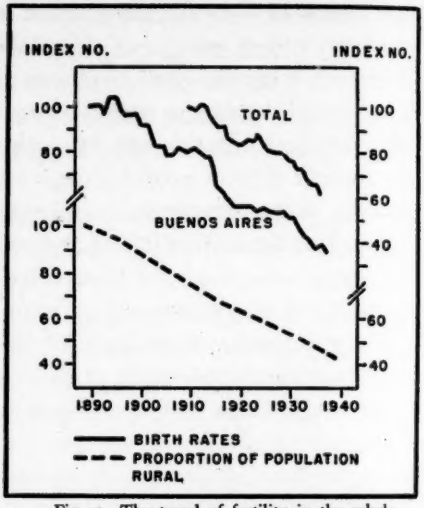


Fig. 5. The trend of fertility in the whole of Argentina and in the Capital, and the trend in the proportion rural (i.e. in places of less than 1,000). Data from Bunge, *op. cit.*, pp. 67, 158; middle line from Bunge's chart, p. 106.

The Value of the City. Our discussion may seem to imply that the fast and somewhat anomalous degree of urbanization in Latin America is harmful. Such an opinion is held by some observers, who reason that the cities represent an excessive cost[22] or that they are bringing about an unexpected and premature maturity.[23] One may argue, however, that it is not the cities themselves, but the peculiar conditions underlying their growth, that should be regretted. Though urbanization in the republics may not reflect as much industrial progress as elsewhere, there can be little doubt that the cities themselves are having a stimulating effect. Their inhabitants are ahead of the rural citizens in nearly every way. As the cities

[21] *Op. cit.*, p. 117.
[22] Schurz, Wm. L.: LATIN AMERICA. New York, Dutton, 1942, pp. 72-73.
[23] Bunge, *op. cit.*, Ch. 4.

increasingly acquire an industrial base, as they link themselves more closely with the hinterland, as they spread out into suburban zones, their influence in the direction of modernization should increase. If they gradually promote a regime of low birth and death rates and thus halt the region's rapid population growth before it reaches a condition of oppressive density, this too will be a benefit. It is perhaps more, rather than less, urbanization that is desirable.

ANNOTATIONS

REHABILITATION OF THE TUBERCULOUS

Doctor Brieger's book[1] presents a quarter century of health experience with the large group of tuberculous expatients and their families who lived and worked at the Papworth Village Settlement. The colony was founded in 1918 by the late Sir Pendrill Varrier-Jones, and the study is a fitting memorial to his pioneering work in the field of the after-care and rehabilitation of the tuberculous.

The scheme at Papworth grew out of the fact that quite a large group of treated tuberculous patients cannot endure the stresses of the competitive labor market without strong hazard to their newly won health. To minimize recurrences, a community for expatients and their families was set up with its hospital, shops, schools, and industries, the latter especially designed to meet the physical and economic requirements of the expatients. At its inception dolorous prophecies were made regarding the effect of such an environment upon the health of the children brought to the Village or born there. It was felt, on the one hand, that meticulous hygienic controls might result in the children's escaping tuberculous infection entirely but that they would be prey to the ravages of a rapidly progressive tuberculosis when they returned to the outside world. Others held that with so many infectious persons about them, the infants could not escape fatal tuberculous meningitis, and the older children, progressive "childhood" tuberculosis. Doctor Brieger shows that neither of these prophecies had substance.

Actually, and this is the main point of the study, no single instance of clinically progressive tuberculosis was encountered among the 108 children born in the Village. Nor did they escape primary tubercu-

[1]Brieger, E. M.: The Papworth Families. A 25 Years' Survey. (With a Preface by Sir Arthur Salusbury MacNalty.) London, William Heinemann — Medical Books, Ltd., 1944, 674 pp., Price 45s.

lous infection, since 42.5 per cent of them showed calcified foci in the lungs on chest roentgen films, 4.6 per cent had other pulmonary residua of the infection, and 1.9 per cent had evidence of a benign "childhood" infection in the making. Six deaths were recorded in the group, four occurring at birth. None of the deaths was caused by tuberculosis.

There were, in addition, 260 children born before admission to Papworth. Most of these had already been exposed in their homes to massive infection. It is not surprising, therefore, that five developed clinically active "childhood" tuberculosis and nine became ill with "adult" pulmonary tuberculosis, all but one case occurring in families with a positive-sputum patient. This incidence of tuberculous disease in "contacts" to positive-sputum source cases is of the same order, the author points out, as that reported by Opie among tuberculous families in Philadelphia.

It is to be regretted some of the data in this study are based upon clinical rather than radiographic findings, and that Moro's tuberculin test was used instead of the more reliable and universally accepted Mantoux test. These are inadequacies which are inherent in any material covering so great a span in years, particularly in the field of tuberculosis, where modern advances in diagnostic techniques have been so great. None the less, the figures concerning the Village-born children, as well as many other related data cited by Doctor Brieger, graphically confirm the beneficial effects of medical supervision, good housing and nutrition, and economic self-sufficiency upon persons living in a properly controlled tuberculous milieu.

At the present time, we have in the United States a few eminently successful rehabilitation and "conditioning" centers for the tuberculous. Their capacity is meager and the need for more of them is recognized. The village settlement scheme has not as yet received a trial here. In relation to our thinking about whether to take up the village scheme, it is important for us to know that contact infection among the children in such an environment does not prevent successful operation.

LOUIS E. SILTZBACH, M.D.